Principles of Pharmacodynamics & Pharmacokinetics

Pharmacodynamics & Receptors

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- What is Pharmacodynamics?
- the study of the physiological effects of drugs (what drugs do to the body)
- study of mechanisms of drug action (drug targets)
- analysis of relationship between drug concentration and effect

Basic questions

- What is a Drug ?
- What are Drug Targets ?

Targets for Drug action

- Drugs are chemicals that affect a physiological system in a specific way
- Most drug targets are proteins: receptors, ion channels, enzymes, carriers
- Specificity & reciprocity. In many cases particular classes of drugs bind only to certain targets & individual targets recognise only certain classes of drugs
- No drugs are entirely specific (ideal) – side effects

Paul Ehrlich (1854-1915)

Synthesised & tested series of organo-arsenic compounds as treatments for syphilis & sleeping sickness.

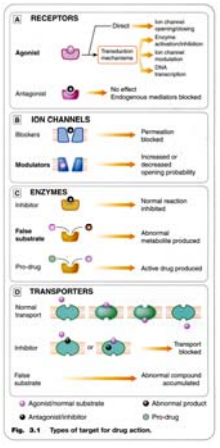
Arsphenamine ("606") marketed by Hoechst in 1910 as *Salvarsan.*

Nobel Prize for Medicine 1908

- Drug actions can be explained by chemical interactions
- A drug will not work unless it is bound (to a target)
- Coined the terms "chemotherapy" and "magic bullet"

Proteins as Drug Targets

- Receptor – protein molecule that recognises endogenous chemical signal. ACh receptor, GABA receptor, β-adrenergic receptor, cytokine receptor, glutamate receptor.
- Ion channel – membrane protein with integral ion channel. Ligand-gated (ionotropic), voltage-gated, G-protein coupled (metabotrobic)
- Enzymes
- Nuclear Receptors
- Transporters



Coupling of drug binding to cellular effects

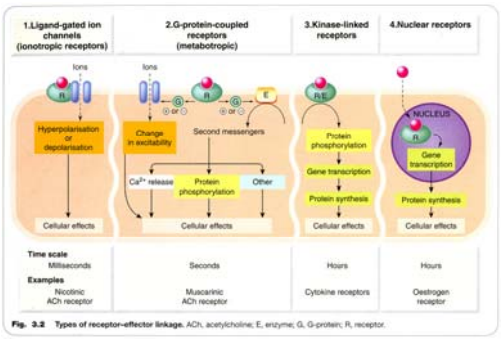
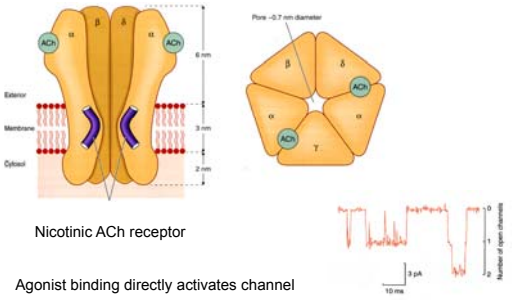


Fig. 3.2 Types of receptor-effector linkage. ACh, acetylcholine; E, enzyme; G, G-protein; R, receptor.

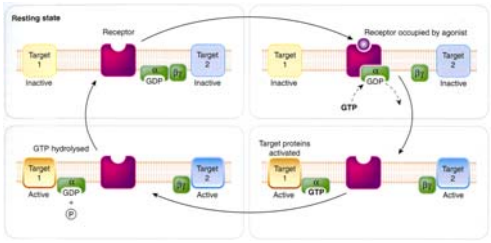
Ligand-gated ion channels



Nicotinic ACh receptor

Agonist binding directly activates channel

G-protein coupled receptors



Agonist binding does not directly activate effector (*e.g.* channel or enzyme) – coupling *via* G-protein α,β,γ subunits, involves hydrolysis of GTP.

Drug-Receptor Interactions

- drug binding and receptor activation are distinct steps
- *Affinity* – measure of drug binding
- *Efficacy* – measure of drug activity

Drug-Receptor Interactions

$$A + R \rightleftharpoons AR \text{ complex}$$

affinity

Affinity – measure of propensity of drug to bind

$$AR \rightleftharpoons \text{effect}$$

efficacy

Efficacy (or intrinisic activity) ability of bound drug to change the activity of the receptor

Drug-Receptor Binding

$$[A] + [R] \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} [AR]$$

k_{+1} rate constant for binding step

k_{-1} rate constant for dissociation of complex

at equilibrium

$$k_{+1}[A][R] = k_{-1}[AR]$$

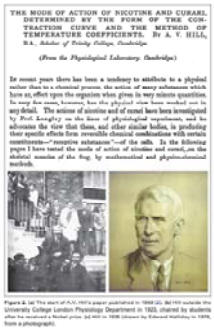
rearranging

$$\frac{[A][R]}{[AR]} = K_D$$

$$K_D = \frac{k_{-1}}{k_{+1}}$$

The lower the K_D the higher the affinity of the drug for receptor

Drug-Receptor Binding


THE MODE OF ACTION OF NICOTINE AND CURARE, DETERMINED BY THE FORM OF THE CONTRACTION CURVE AND THE METHOD OF TEMPERATURE COEFFICIENTS. By A. V. HILL, B.A., Scholar of Trinity College, Cambridge.

(From the Physiological Laboratory, Cambridge.)

Colquhoun, D. TIPS, 27, 149 (2006)

$$p_A = \frac{[AR]}{[AR]+[R]}$$

$$p_A = \frac{[A]}{[A]+K_D}$$

Hill-Langmuir equation

$$B = \frac{B_{max}[A]}{[A]+K_D}$$

Derivation of Hill-Langmuir Equation

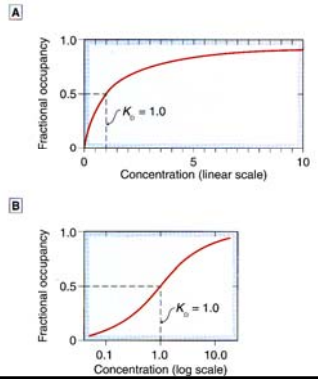
$$[A] + [R] \underset{}{\overset{K_D}{\rightleftharpoons}} [AR]$$

$$\frac{[A][R]}{[AR]} = K_D \qquad R_{total} = [R] + [AR]$$

$$p_A = \frac{[AR]}{R_{total}} = \frac{[AR]}{[R]+[AR]} = \frac{[AR]}{\frac{K_D[AR]}{[A]}+[AR]}$$

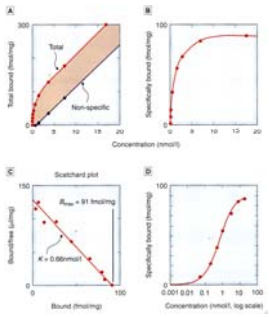
$$p_A = \frac{1}{\frac{K_D}{[A]}+1} = \frac{[A]}{K_D+[A]} = \frac{B}{B_{max}}$$

Hill-Langmuir equation



$$p_A = \frac{[A]}{[A]+K_D}$$

Calculating B_{max} & K_D from experimental data



$$B = \frac{B_{max}[A]}{[A]+K_D}$$

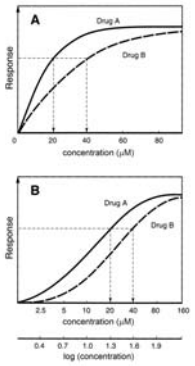
$$[A]\ (B_{max} - B) = BK_D$$

$$\frac{B}{[A]} = \frac{B_{max}}{K_D} - \frac{B}{K_D}$$

Scatchard equation

B_{max} total number of binding sites in preparation

Concentration response curves



Example of two drugs A & B. Drug A is twice as potent as drug B.

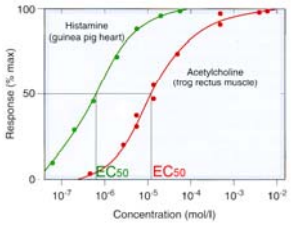
Plotting concentration response on log scale transforms hyperbola to sigmoid curve. Middle section ~linear.

Drugs acting in similar ways with different potencies give parallel shifts

e.g in this case shift is log (2) = 0.3 log units

Hill Equation

Empirical relationship between concentration and response



$$y = \frac{y_{max}[x]^n}{[x]^n + EC_{50}{}^n}$$ General form

$$\text{response} = \frac{100 \times [\text{agonist}]^n}{[\text{agonist}]^n + EC_{50}{}^n}$$

EC_{50} – concentration for 50% effect

n (or n_h) – Hill coefficient

Drug *potency* is sometimes defined as the reciprocal of the EC_{50}

Cumulative dose response from a population

Physiological end point (30% increase in heart rate)

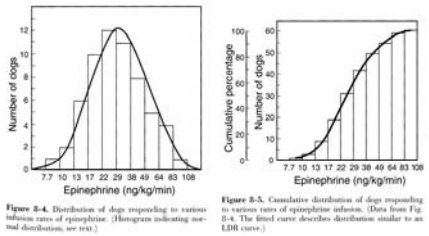


Figure 8-4. Distribution of dogs responding to various infusion rates of epinephrine. (Histogram indicating normal distribution; see text.)

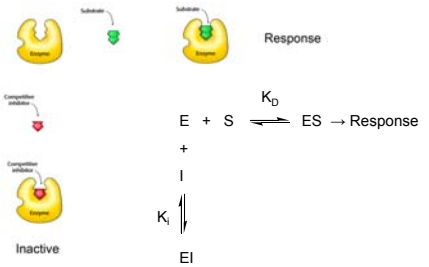
Figure 8-5. Cumulative distribution of dogs responding to various rates of epinephrine infusion. (Data from Fig. 8-4. The fitted curve describes distribution similar to an LDR curve.)

The steepness of the curve (n) reflects the heterogeneity of the population. Steep curve (large n) – homogeneous population.

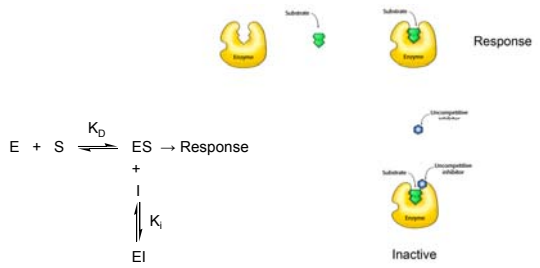
Receptor Antagonism

- Competitive Antagonism
  - Inhibitor and agonist compete (cannot bind at the same time)
- Uncompetitive Antagonism
- Mixed Antagonism
- - Non-competitive Antagonism

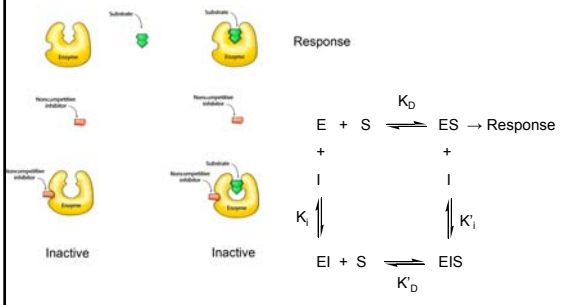
Competitive antagonism (competitive inhibition)



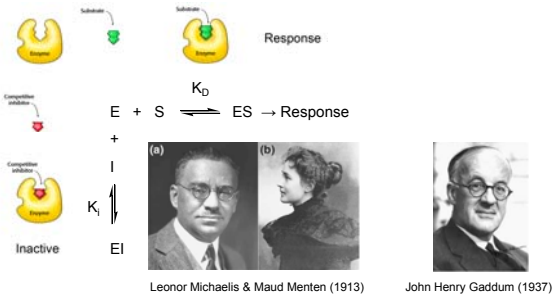
Uncompetitive Antagonism



Non-competitive antagonism



Competitive antagonism (competitive inhibition)



Leonor Michaelis & Maud Menten (1913)

John Henry Gaddum (1937)

Michaelis-Menten Equation

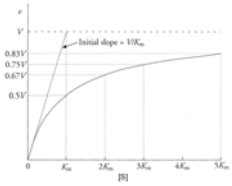
$$v = \frac{k_{cat} e_0 [S]}{K_M + [S]}$$

Fundamental equation of enzyme kinetics

Relates reaction rate, *v*, to substrate concetration and the Michaelis constant K_M

$$v = \frac{V_{max}[S]}{K_M + [S]}$$

Can be written in this form where V_{max} is the maximum reaction rate



Maths revision: rectangular hyperbola

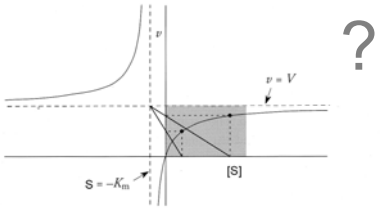


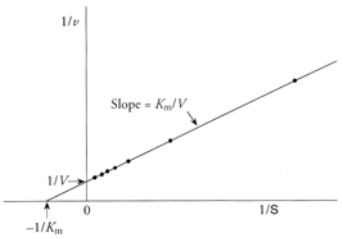
Figure 2.2. Dependence of initial rate v on the substrate concentration **S** for a reaction obeying the Michaelis–Menten equation. The part of the curve from $S = 0$ to $5K_m$, the shaded part of the Figure, is the same as in Figure 2.1, but the range of values shown is much wider and includes physically impossible values, in order to illustrate the relationship of the curve to the two asymptotes, which intersect at the point $(-K_m, V)$.

Double-Reciprocal Plot

Lineweaver-Burke plot

$$v = \frac{V_{max}[S]}{K_M + [S]}$$

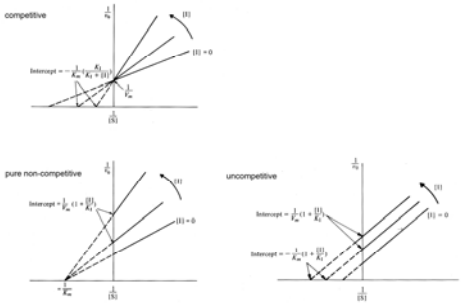
$$\frac{1}{v} = \frac{K_M}{V_{max}} \times \frac{1}{[S]} + \frac{1}{V_{max}}$$



Characterising type of inhibition from double reciprocal plot with and without inhibitor

type of inhibition	apparent V_{max}	apparent K_M
Competitive	V_{max}	$K_M(1 + [I]/K_i)$
Pure non-competitive	$V_{max} / (1 + [I]/K_i)$	K_M
Uncompetitive	$V_{max} / (1 + [I]/K_i)$	$K_M / (1 + [I]/K_i)$

Characterising type of inhibition from Lineweaver-Burk plot with and without inhibitor



Lineweaver-Burk plot showing inhibition of luciferase enzyme by the volatile anaesthetic halothane

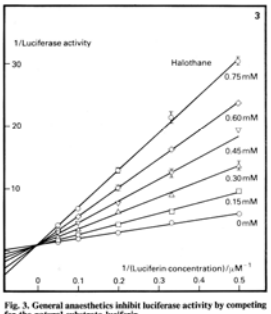
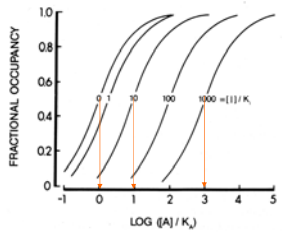


Fig. 3. General anaesthetics inhibit luciferase activity by competing for the natural substrate luciferin.

Franks, NP & Lieb WR (1985) Chemistry in Britain v21, p919

Schild analysis of competitive antagonism

occupancy of receptor by agonist A, in presence of competitive antagonist B



$$p_A = \frac{[A]}{[A] + K_A}$$

$$p_A = \frac{[A']}{[A'] + K_A(1 + [I]/K_i)}$$

$$dr = \frac{[A']}{[A]} = \frac{[I]}{K_i} + 1$$

Schild equation

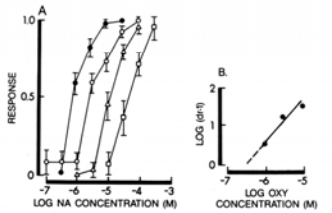
dose ratio (dr)
- depends only on K_i of antagonist, not size of reference response or agonist K_A
- increases linearly with antagonist concentration [I]

Schild equation holds true if

- The observed response is the same if the occupancy of each site by A is the same, regardless of how many receptors are occupied by antagonist
- Binding of antagonist, I, and agonist, A, are mutually exclusive (competitive inhibition)
- Antagonist does not change receptor conformation (not inverse agonist)
- Antagonist has same affinity for each binding site
- Measurements are at equilibrium

Schild plot

$$\log(dr - 1) = \log[I] - \log[K_i]$$



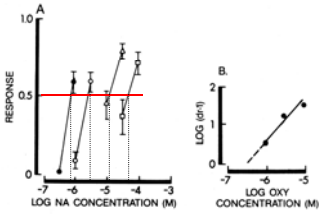
$$dr = 2$$
$$\Rightarrow \log(dr - 1) = 0$$
$$\therefore \log[I] = \log[K_i] = -pK_i$$

Here pK_i=6.5, K_i = 0.316mM

NA – noradrenaline; OXY- oxymetazoline (antagonist)

Schild plot

$$\log(dr - 1) = \log[I] - \log[K_i]$$



Null method, works with partial concentration-response curves

Provided response is the same for given agonist occupancy works for complex mechanisms

(eg GPCR)

Affinity & Efficacy

Efficacy

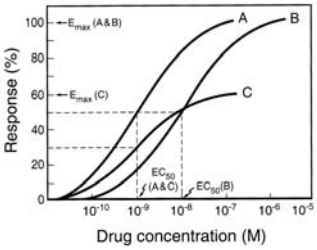
$$AR \underset{}{\overset{E}{\rightleftharpoons}} AR^* \rightarrow \text{effect}$$

bound (inactive) bound (active)

Efficacy, E, describes transition from receptor with agonist bound (inactive) to receptor with agonist bound (active).

Different agonists (drugs) may have different efficacies

Full & Partial Agonists



Full agonist E_{max} = 100%

Partial agonist E_{max} < 100%

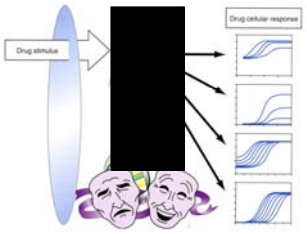
In this example A & B are full agonists, while C is a partial agonist.

B is less potent than A (greater EC_{50}).

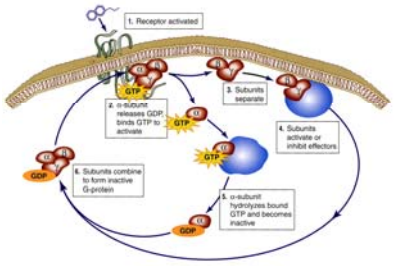
The potency of C is the same as A, but the efficacy of C is less than A.

Classical treatment assumes agonist binding (affinity) and efficacy are discrete entities

"Classical" Pharmacology



Inside the Black Box

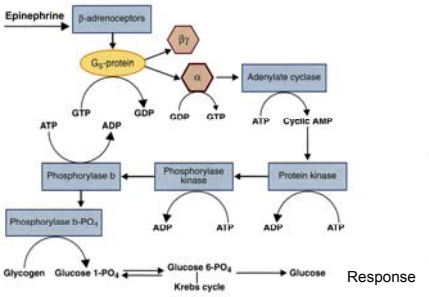


Inside the Black Box

Actvation of drug-bound receptor AR→AR*

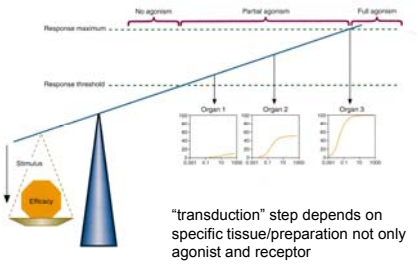
(intrinsic efficacy)

"transduction"



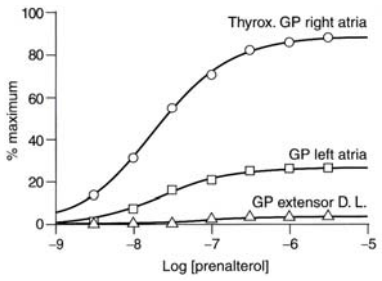
Response

FIGURE 2.8 Stimulus response cascade for the production of blood glucose by activation of β-adrenoceptors.

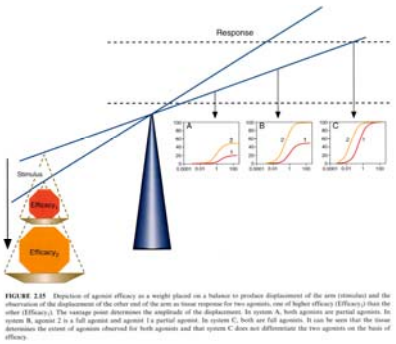


"transduction" step depends on specific tissue/preparation not only agonist and receptor

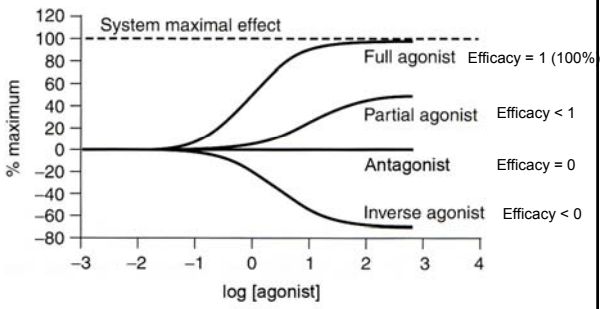
Same drug can be apartial agonist or a full agonist in different preparations from guinea pig



Prenalterol; β-adrenoceptor agonist. D.L. – digitorum longus



"Classical" Pharmacology



What do we mean by "inverse agonist"?

Some receptors are *constitutively* active

they have a baseline activity in the *absence of agonist*