Pharmacodynamics for the prescriber

Simon RJ Maxwell

Abstract

Pharmacodynamics is the study of how drugs have effects on the body. The most common mechanism is by the interaction of the drug with tissue receptors located either in cell membranes or in the intracellular fluid. The extent of receptor activation, and the subsequent biological response, is related to the concentration of the activating drug (the agonist). This relationship is described by the dose–response curve, which plots the drug dose (or concentration) against its effect. This important pharmacodynamic relationship can be influenced by patient factors (e.g. age, disease) and by the presence of other drugs that compete for binding at the same receptor (e.g. receptor antagonists). Some drugs acting at the same receptor (or tissue) differ in the magnitude of the biological responses that they can achieve (i.e. their efficacy) and the amount of the drug required to achieve a response (i.e. their potency). Drug receptors can be classified on the basis of their selective response to different drugs. Constant exposure of receptors or body systems to drugs sometimes leads to a reduced response (i.e. desensitization).

Keywords Affinity; agonist; antagonist; desensitization; dose–response curve; pharmacodynamics; receptors; selectivity; therapeutic index

Key points

- Most drugs exert their effects by binding to receptor proteins (e.g. channel-linked, G-protein-coupled, kinase-linked, DNA-linked) located in cell membranes or nuclei, although there are many other drug targets (e.g. enzymes, voltage-gated channels, transport proteins)
- Drugs that activate receptors to produce a biological response are known as agonists, whereas those that bind the same receptors but do not cause biological responses are known as antagonists
- The relationship between drug dose and biological response is called the dose–response curve and is normally plotted on a logarithmic dose scale, appearing as a sigmoid curve
- Agonists and antagonists compete for receptor binding, and the presence of antagonists shifts the dose–response curve of the agonist to the right. The presence of increasing antagonist concentration moves the curve further to the right
- The efficacy of a drug is a measure of its capacity to produce a biological effect (the maximum effect being known as E_{max}), and the potency of a drug is an expression of the amount of a drug required to produce biological effects (normally expressed as the ED_{50}, the dose required to produce 50% of E_{max})
- The therapeutic index is the ratio between the dose of a drug that causes adverse effects and the dose that achieves therapeutic benefits
- Desensitization to drugs is a common phenomenon; when it occurs rapidly it is known as tachyphylaxis, and when it occurs more slowly it is known as tolerance

What is meant by the term 'pharmacodynamics'?

Pharmacodynamics is the study of:

- the biochemical and physiological effects of drugs on the body
- the mechanisms of drug action
- the relationship between drug concentration and drug effect.[1,2]

Pharmacodynamics can be simply described as the study of 'what a drug does to the body'. Basic pharmacodynamic studies involve exposing cells or tissues to constant concentrations of a drug and observing their effect. For prescribers, the situation is more complex, because drug exposure depends on how effectively drug molecules are taken into the body and reach their site of action (absorption, distribution) and how quickly they are removed from the body (metabolism, excretion). These processes are collectively known as pharmacokinetics (the study of 'what the body does to a drug').

What are the ways in which drugs produce effects in body systems?

The pathophysiology underlying the progression of most diseases involves the disordered structure and function of cells and tissues, which are composed of complex molecules and biochemical processes. Drugs are intended to restore normal function by acting on 'target molecules' in the affected tissue or organ. Binding exerts a biological effect, either by initiating new events or by blocking the actions of endogenous substances (e.g. neurotransmitters, hormones). Resulting effects include changing the ion content of cells, promoting the secretion of hormones, reducing electrical signalling by excitable cells, reducing contractile activity, stimulating the synthesis of new proteins, and many others. Many of these responses result from interactions between drugs and endogenous 'receptors'.

Simon RJ Maxwell *MB ChB MD PhD FRCP FRCPE FHEA is Professor of Student Learning (Clinical Pharmacology and Prescribing) at the University of Edinburgh and Honorary Consultant Physician at the Western General Hospital, Edinburgh, UK. His main research interests relate to the causes and prevention of prescribing errors with particular emphasis on the importance of training and assessment of junior prescribers. He is Medical Director of the UK Prescribing Safety Assessment. Competing interests: none declared.*

What are receptors?

Receptors are typically glycoproteins located in cell membranes that specifically recognize smaller molecules (including drugs) that are capable of binding ('ligating') themselves to the receptor protein. This binding initiates a conformational change in the receptor protein leading to a series of biochemical reactions inside the cell (signal transduction), often involving the generation of 'secondary messengers', that is eventually translated into a biological response (e.g. muscle contraction, hormone secretion) (Figure 1). Although the ligands of interest to prescribers are exogenous compounds (i.e. drugs), receptors in human tissues have evolved to bind endogenous ligands such as neurotransmitters, hormones and growth factors. Formation of the drug–receptor complex is usually reversible, and the proportion of receptors occupied (and thus the response) is directly related to the concentration of the drug. Reversibility enables biological responses to be modulated and means that similar ligands can compete for access to the receptor. The term 'receptor' is usually restricted to describing proteins whose only function is to bind a ligand; however, it is sometimes used more widely in pharmacology to include other kinds of drug target such as voltage-sensitive ion channels, enzymes and transporter proteins (Figure 1).[1,2]

How do receptors mediate pharmacological responses?

The main types of drug targets and their mechanisms of action are described in Table 1.

What is meant by 'receptor affinity'?

Affinity of ligands is a function of both the rate of association and the rate of dissociation of the ligand–receptor complex;[3] the former depends on the 'goodness of fit' at a molecular level, whereas the latter depends on how tightly the ligand is bound (the strength of the chemical bond). Systems requiring rapid fine modulation (e.g. nerve synapses) must have agonists with a low receptor affinity because those with high receptor affinity would produce unnecessarily prolonged responses. During stimulation, the agonist concentration near the receptor must be relatively high, but the agonist is then cleared rapidly by active transport. In contrast, growth factors are typically peptides with very high affinity for their receptors, and achieve their effects at concentrations that are difficult to detect in vivo.

What do the terms agonist, antagonist and partial agonist mean?

Receptor ligands can be distinguished on the basis of their potential to initiate a biological response following receptor binding:

- **Agonists** bind to a receptor protein to produce a conformational change, which initiates a signal that is coupled to a biological response. As the free ligand concentration increases, so does the proportion of receptors occupied, and hence the biological effect. When all the receptors are occupied, the maximum response is achieved.
- **Antagonists** bind to a receptor but do not produce the conformational change that initiates an intracellular signal. Occupation of the receptor by a *competitive antagonist* prevents binding of other ligands and so 'antagonizes' the biological response to the agonist. The inhibition that antagonists produce can be overcome by increasing the dose of the agonist. Some antagonists interfere with the response to the agonist in ways other than receptor competition and are known as *non-competitive antagonists*. Simply increasing the dose of the agonist cannot overcome their effects, so the maximum response to the agonist (its efficacy) is reduced.
- **Partial agonists** are able to activate a receptor but cannot produce a maximal signalling effect equivalent to that of a full agonist even when all the available receptors are occupied.

What is the relationship between drug dose and response?

When the relation between drug dose (*x*-axis) and drug response (*y*-axis) is plotted on a base 10 logarithmic scale, this produces a sigmoidal dose–response curve (Figure 2a). Clinical responses that might be plotted in this way include change in heart rate,

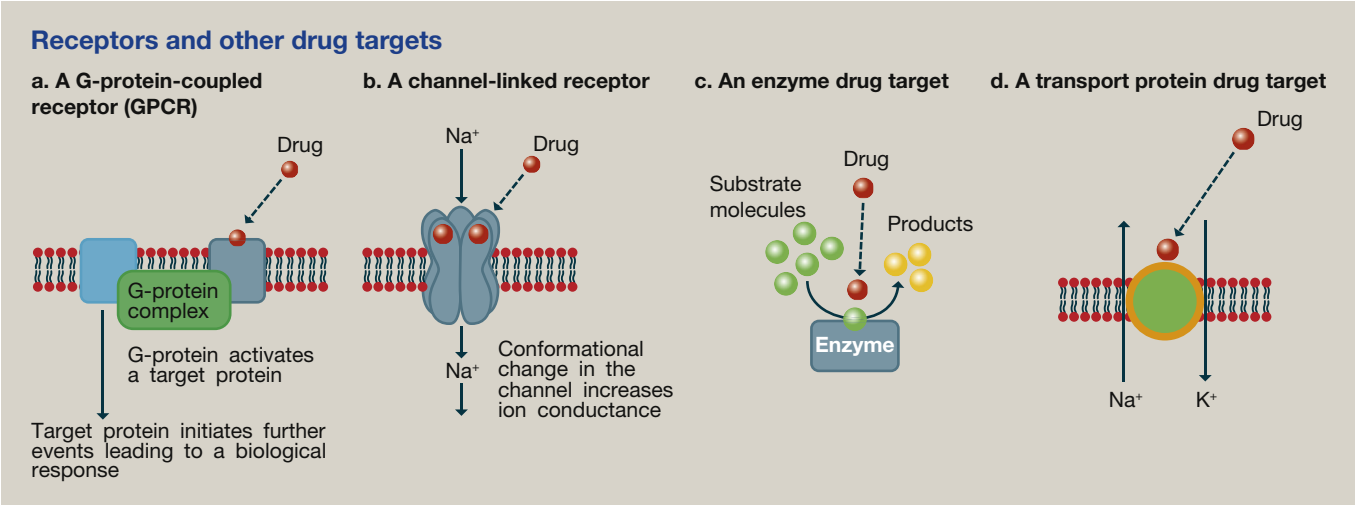

Figure 1