Update in
Anaesthesia

Pharmacodynamics and Receptor Physiology

James Noblet
Correspondence Email: james.noblet@gmail.com

Summary

- Pharmacodynamics illustrates what a drug does to the body.
- Drugs act on 'targets' by binding.
- The equilibrium between bound and unbound targets (affinity) helps to determine a drug's effect.
- Receptors are a special type of target, involved in the body's normal signalling processes.
- Receptors can be activated, partially activated or inactivated when bound by a drug (efficacy).
- Plotting log drug dose against response produces curves which differ, depending on affinity, efficacy and the presence of other drugs.

INTRODUCTION

Pharmacodynamics describes the processes through which a drug brings about its effect in the body. To begin to comprehend this, we must start by breaking down the interaction to a molecular level and create models to further our understanding. The fundamental principle behind a drug's action is that to cause effect, it must interact with its target.

TARGETS

These are endogenous macromolecules which play some role in regulating the body's normal physiological processes. The word target is a generic term for the site where any individual drug creates its actions. They can be broadly classified into four types, depending on the function they normally serve:

1. **Receptors** e.g. adrenergic receptors targeted by adrenaline (epinephrine)
2. **Ion channels** e.g. voltage gated Na+ channels targeted by lidocaine
3. **Enzymes** e.g. Acetylcholinesterase targeted by neostigmine
4. **Carrier molecules** e.g. Noradrenaline (norepinephrine) uptake-1 targeted by tricyclic antidepressant drugs.

Confusion can arise at this point over the interchangeable use of the term '*receptor*'. The word receptor has been used as a general term for the molecular site of action of any drug (described here as a target) or more specifically as a cell membrane associated structure involved in the transduction of an endogenous signalling process (one particular target sub-type); the latter use is applied here. This account of pharmacodynamics will describe the general principles which apply to all drug–target interactions before moving on to the specific interactions a drug can have with a receptor.

DRUG–TARGET INTERACTION

This implies a coming together of the drug with its target or more specifically a small part of the target. The drugs atomic configuration must allow it to bind with the target, analogous to a key (drug) fitting a lock (target). The need for this spatial symmetry explains why individual isomers of the same drug can produce different effects – without the right shape the key will not fit the lock. The term binding represents the idea that the drug and target are now considered 'joined' and are no longer two separate entities. The exact nature of this adherence is not important other than its potential reversibility - the possibility they could exist separately again.

The binding process somehow induces a change in the behaviour of the target molecule, which brings about the drugs affects. In order to be clinically useful a drug needs to demonstrate specificity for the target it interacts with. It should be noted that drugs can bind to structures that are not in the four groups listed without producing clinical effects, and that there are drugs whose target has yet to be discovered. The majority of drugs can be assumed to work in this way although some produce their effects through physiochemical means alone.

DRUG–TARGET KINETICS

For reversible drug–target interactions a dynamic equilibrium exists:

$$\text{Drug (D)} + \text{Target (R)} \leftrightarrow \text{Drug-Target (DR)}$$

$$D + R \leftrightarrow DR$$

This 'first principle' allows further manipulation to produce many mathematical formulae describing the concepts of pharmacodynamics.

The position of the equilibrium is described by K_D, the equilibrium constant (also referred to as the dissociation constant), which is the ratio of the dissociated forms to the associated form:

$$K_D = \frac{[D] \times [R]}{[DR]}$$

The affinity constant of a drug indicates how readily it will bind to its target and is the reciprocal of the equilibrium constant ($1/K_D$).

RECEPTORS

The human body has evolved multiple ways for communication within and between its own various

James Noblet
Anaesthetic Registrar
The Royal National
Orthopaedic Hospital
Stanmore
Middlesex
HA7 4LP
UK

organ systems. Put very simply, signals are sent from one place and received in another which contributes to the maintenance of homeostasis, facilitating whatever change is necessary at that time.

Receptors are involved in the receiving and further processing (transduction) of these endogenous signals, and as such are one of the main targets for drugs, either by creating a signal which was not there naturally, through drug–receptor interaction, or acting as a blocker to the body's own signals.

Generally they are proteins found in cell membranes that selectively interact via a specific binding site with a molecule from the extracellular environment (ligand). When these ligands occur naturally, binding to a specific receptor transmits the intended signal. One ligand may bind to multiple different receptor types bringing about contrasting effects at each.

There are four types of receptor, classified on their normal mode of action:

Ligand gated ion channels (Figure 1)

These receptors undergo a conformational change after the natural ligand binds to its recognition site on the extracellular portion of the receptor. This opens a pore in the cell membrane through which ions can travel. The exact nature of the ion depends on the receptor itself, the direction of travel being determined by the concentration gradient.

Nicotinic acetylcholine receptors found at the neuromuscular junction are an example. The binding of two acetylcholine molecules opens a non-selective cation channel which allows Na^+ ions to flow in, down its large concentration gradient.

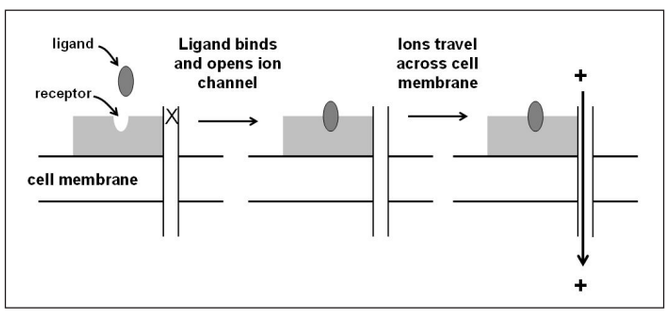

Figure 1. *A ligand gated ion channel*

G-protein coupled receptors (Figure 2)

These are receptors made of multiple associated sub-units which span the cell membrane. Again, activation begins with the attachment of a ligand to a specific extracellular binding site. This enables a change in the arrangement of the receptors constituent parts, which in turn, leads to an alteration in the activity of a specific intracellular enzyme (either adenylate cyclase or phospholipase C). The displacement of guanine diphosphate (GDP) by guanine triphosphate (GTP) from the receptor complex is integral to this process, hence the term 'G-protein'. A change in enzyme activity will alter the concentration of the enzymes substrates, mediating the response to the initial signal. This is a much slower process which relies on 2nd messengers (the intracellular substances) to amplify the external signal, as part of a biological cascade.

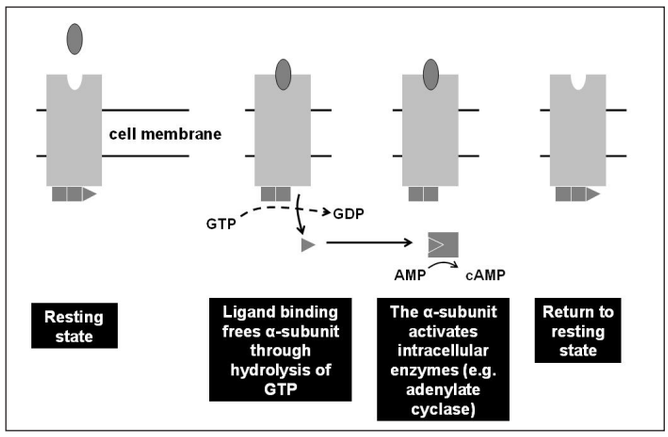

Figure 2. *A G-protein coupled receptor*

Tyrosine kinase receptors

These mediate the action of insulin and a variety of growth factors. Extracellular ligand binding activates intracellular tyrosine kinase, phosphorylating various target proteins.

Intracellular receptors

Lipid soluble ligands are able to cross the cell membrane and activate nuclear receptors which in turn alter DNA transcription. Steroid receptors are an example.

DRUG–RECEPTOR INTERACTIONS AND RESPONSE

The next section of this article describes examples to demonstrate the specifics of drug–receptor interactions.

In order to cause an effect, a drug's first step is binding to its receptor and the second is inducing some form of change. The overall effect a drug can have will depend on the proportion of receptors available that are occupied (bound by) the drug; if all receptors are occupied, then that drug must be exerting its own maximum possible effect. The fraction of occupied receptors (f) can be described mathematically using the principles of drug–target kinetics, and dividing receptors to those occupied and those that are not:

Total Receptors (Rt) = Free Receptors (R) + Drug-Receptor complexes (DR)

This can be re-arranged to show that:

$$f = \frac{[D]}{K_D + [D]}$$

Figure 3 demonstrates this relationship graphically. As the drug concentration rises, the fraction of receptors occupied increases and approaches 1. This is an example of a rectangular hyperbola. Since response is directly proportional to the fractional occupancy, the y axis can be re-labelled as response, giving a dose-response curve. When half the receptors are occupied then the drug concentration is equal to the dissociation constant.

Another important concept is that of intrinsic activity, this describes the ability of the drug to produce a response from its receptor after it has bound. It is also known as efficacy and represents the magnitude of effect the drug can have, ranging from 0 (no effect) to 1 (maximal possible effect on that receptor). A drug which combines with its

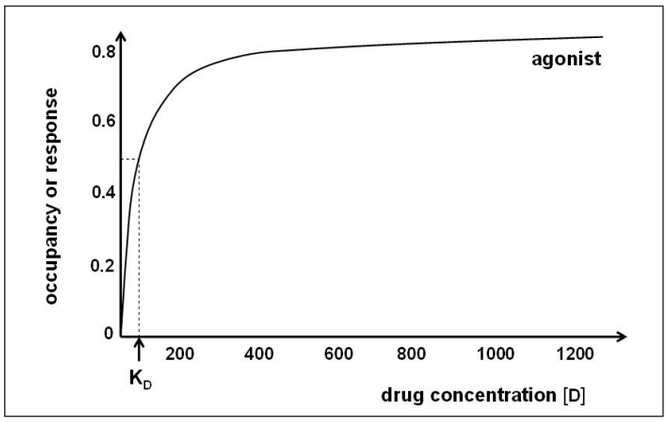

Figure 3. *Dose response curve of an agonist at a receptor*

receptor to give a maximal effect is an agonist - the 'key turns in the lock'. One which has no activity when bound but prevents the receptor being activated by other means is an antagonist – the 'key blocks the lock'. Any drug which produces a response, but less than the maximal response possible from that tissue is a partial agonist.

The response to a drug is therefore governed by the fraction of receptors occupied, combined with the drug's efficacy once bound.

Dose–response curves (Figure 4)

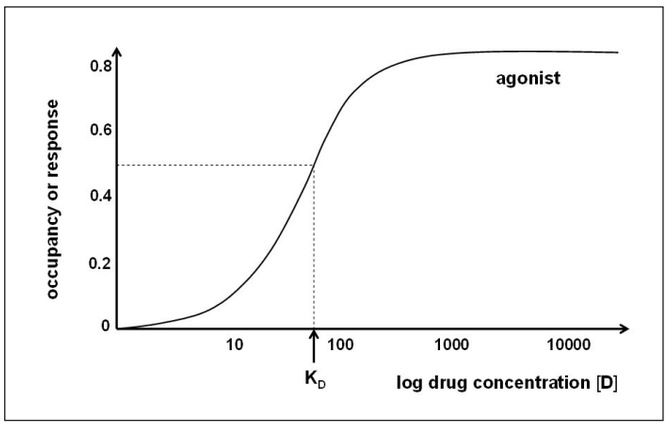

Figure 4. *Log dose-response curve. Changing the x-axis to a log scale transforms the rectangular hyperbola of Figure 3 into a much more user friendly sigmoid shape, with an almost linear middle section*

This curve can be used to demonstrate graphically all the various principles that underlie drug–receptor physiology – affinity, antagonism and partial agonism:

Affinity (Figure 5)

K_D, the dissociation constant, can be derived from the graph, as it equals the drug dose which gives 50% receptor occupancy. As some receptors bind more than one drug, differences in the affinity the drugs have for the receptor can be demonstrated. A drug with a lower affinity (but equal efficacy) has its log dose response curve shifted to the right. The two curves are parallel; for an equal amount of drug, a higher proportion of receptors are occupied by drug A than drug B, as A has a greater affinity. The same level of occupancy (and hence response) can be achieved with B, it just requires more drug to do so.

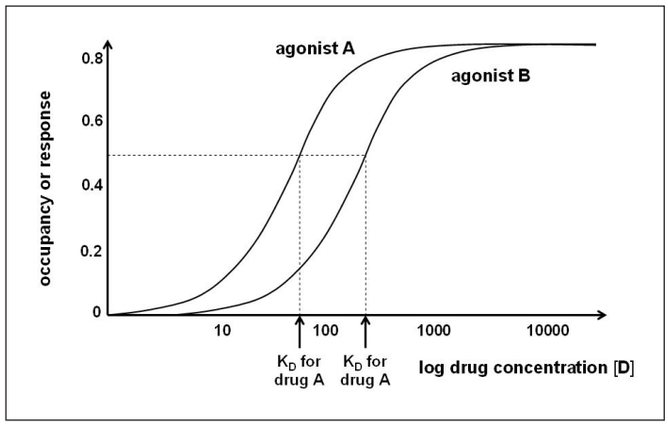

Figure 5. *Log dose-response curve with varying affinity*

Competitive antagonism

A similar situation can occur if there is competition for a receptor's binding site between agonist and antagonist drugs. In order to activate the receptor the agonist must bind as normal, but now it faces competition from the antagonist. The only effect the antagonist produces is to block the agonist, hence in the presence of an antagonist, more agonist must be added to illicit the same effect. Figure 6 shows that the conventional log-dose response curve for an agonist undergoes a parallel shift to the right when a fixed dose of competitive antagonist is added.

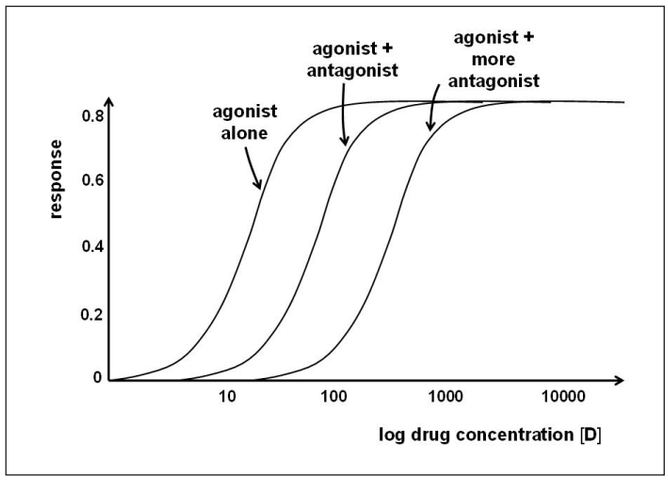

Figure 6. *Log dose-response with competitive antagonism*

Non-competitive antagonism

This occurs when an antagonist targets a different portion of the receptor to the agonist, and in doing so, somehow alters the receptors properties. The affinity the agonist has for its own binding site is the same but the effect the drug can have is now reduced. The agonist is not competing with the antagonist, so adding more agonist will never fully overcome its effect. Figure 7 shows that in the presence of a fixed dose of non-competitive antagonist the slope of the curve is flattened, but its position (K_D) remains the same.

Irreversible competitive antagonism

Up to now we have been talking about reversible drug-receptor

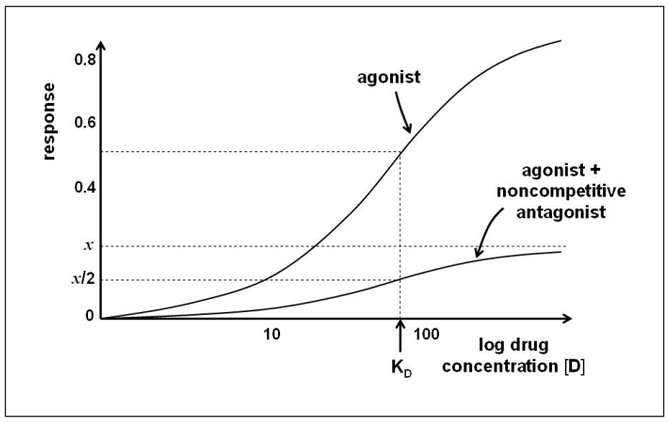

Figure 7. *Log dose-response curve with non-competitive antagonism*

interactions, but what happens when an antagonist binds a receptor and won't let go? This occurs if covalent bonds form, which are very strong and are not easily broken.

As the concentration of antagonist rises, more receptors become blocked irreversibly. This leaves fewer receptors for the agonist to work with, so its maximal effect is reduced permanently, as no amount of agonist can undo the antagonist-receptor bond. The affinity the agonist has for the remaining free receptors is unchanged. This is shown in Figure 8; there is a downward shift representing a reduced effect, but K_D remains the same.

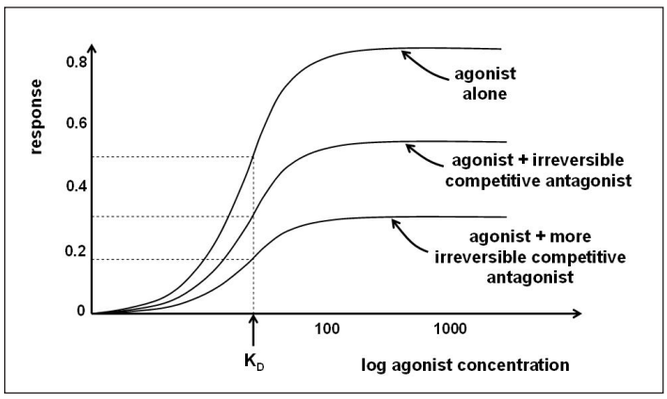

Figure 8. *Log dose-response with irreversible competitive antagonism*

Partial agonists

As previously defined, a partial agonist binds reversibly to a receptor eliciting an effect, but not the maximum possible effect. Different drugs can activate the same receptor but with varying efficacy. Figure 9 is a comparison of the log dose–response curves for an agonist and a partial agonist. The partial agonist can never generate a full response, so its final position will always be below that of the agonist. The two drugs could have the same affinity for their common receptor, but in general drugs that have a lower efficacy also have a lower affinity.

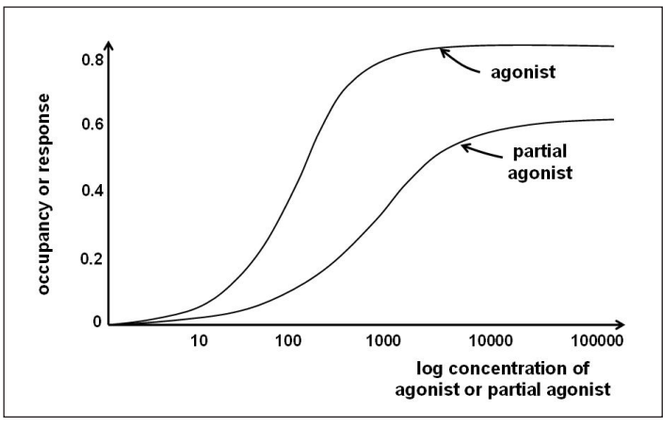

Figure 9. *Log dose-response with partial agonist*

When mixed together, a partial agonist and an agonist will compete for the same binding site, with the overall effect being dependant on which drug predominantly occupies the receptor. Figure 10 illustrates this situation by comparing the log dose–response curves for a partial agonist with four different (but constant) concentrations of agonist also present. As more partial agonist is added it occupies more of the receptors until the response seen is purely down to the partial agonist. If agonist activity was present to begin with, the response may be reduced by the addition of partial agonist as it competes with and replaces the agonist.

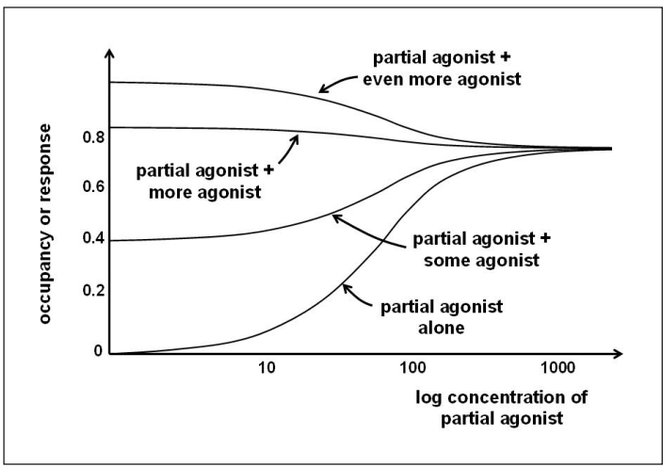

Figure 10. *Log dose-response for partial agonist with agonist*

SUMMARY

This classical theory provides a basis for understanding the relationship between binding and effect. There are many examples where this model does not fit and some of the ideas are not universally accepted. It is not the whole picture and should be seen as an introduction to the principles involved.