There are four principle protein targets with which drugs can interact: enzymes (e.g. neostigmine and acetyl cholinesterase), membrane carriers (e.g. tricyclic antidepressants and catecholamine uptake-1), ion channels (e.g. nimodipine and voltage-gated Ca$^{2+}$ channels) and receptors. This article is concerned with the receptor and describes the dynamics of drug-receptor interaction, agonists, antagonists, partial agonists and inverse agonists, efficacy and potency. Key definitions are shown in Table 1.

**Receptors**

A receptor can be defined loosely as ‘a molecule that recognizes specifically a second small molecule whose binding brings about the regulation of a cellular process…in the unbound state a receptor is functionally silent’. This definition states that a receptor binds specifically a particular ligand (e.g. bombesin binds to bombesin receptors and not vanilloid receptors) but in reality selectivity is a more accurate definition as in some cases high concentrations of ligands will bind to multiple receptor types. The caveat that in the unbound state a receptor is silent holds true in most cases (particularly those encountered with current clinically useful drug-receptors) but an exception can be used to explain inverse agonism.

Receptors can be subdivided into four main classes: ligand-gated ion channels, tyrosine kinase-coupled, intracellular steroid and G-protein-coupled (GPCR). Basic characteristics of these receptors along with some drugs that interact with each type are shown in Table 2.

The nicotinic acetylcholine receptor should be a familiar member of the ligand-gated ion channel family to all anaesthetists as this is the site of action for neuromuscular blocking agents. The receptor (as is characteristic of this family) is composed of multiple subunits that come together to form an aqueous pore through which (not only) Na$^{+}$ ions flow. Binding of acetylcholine opens the pore allowing Na$^{+}$ influx to produce a depolarization. Other examples of this family include the GABA$\alpha$ receptor (a major target for anaesthetic action) whose activation allows Cl$^{-}$ influx to produce membrane hyperpolarization and reduced central transmission.

Tyrosine kinase-coupled and steroid receptors are of little direct anaesthetic relevance and will not be considered further in this article. Anaesthetic steroids (e.g. alphaxalone) do not produce anaesthesia via the steroid receptor; they potentiate the actions of GABA$\alpha$ at the GABA$\alpha$ receptor. GPCRs are an important class encompassing some of the major systems used/manipulated clinically in the

<table>
<thead>
<tr>
<th>Key points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ligand-gated ion channels and G-protein-coupled receptors are important in anaesthesia.</td>
</tr>
<tr>
<td>Agonists bind to receptors to produce a functional response.</td>
</tr>
<tr>
<td>Agonists can be full, partial or inverse.</td>
</tr>
<tr>
<td>Antagonists reverse the effects of agonists.</td>
</tr>
<tr>
<td>Antagonists can be competitive or non-competitive.</td>
</tr>
</tbody>
</table>

**Table 1** Key definitions

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_D$</td>
<td>The equilibrium dissociation constant represents the concentration of radioligand occupying half of the maximum receptor population. $K_D$ is a measure of affinity</td>
</tr>
<tr>
<td>$B_{max}$</td>
<td>The total number of receptors in a particular tissue.</td>
</tr>
<tr>
<td>Potency</td>
<td>Crudely defined as the dose range over which a response is produced</td>
</tr>
<tr>
<td>$ED_{50}$</td>
<td>The dose of drug producing half the maximum response and is a simple measure of potency</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Crudely defined as the size or strength of a response produced by a particular agonist in a particular tissue</td>
</tr>
<tr>
<td>$E_{max}$</td>
<td>Maximum response a particular agonist can produce in a particular tissue and is a crude measure of efficacy</td>
</tr>
</tbody>
</table>

**Table 2** Basic receptor characteristics

<table>
<thead>
<tr>
<th>Location</th>
<th>LGIC</th>
<th>TRK</th>
<th>Steroid</th>
<th>GPCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main action</td>
<td>Ion flux</td>
<td>Phosphorylation</td>
<td>Gene transcription</td>
<td>2nd messengers</td>
</tr>
<tr>
<td>Example/drug</td>
<td>Nicotinic/NMBD</td>
<td>Insulin/insulin</td>
<td>Steroid/thyroxine</td>
<td>Opioid/morphine</td>
</tr>
<tr>
<td></td>
<td>NMDA/ketamine</td>
<td>Growth factor/EGF</td>
<td>Steroid/oestrogen</td>
<td>Adrenoceptor/isoeprenaline</td>
</tr>
</tbody>
</table>

LGIC = ligand-gated ion channel; TRK = tyrosine kinase coupled; GPCR = G-protein-coupled receptor; NMBD = neuromuscular blocking drugs; NMDA = N-methyl-D-aspartate; EGF = epidermal growth factor.
Drugs and receptors

Anaesthetic setting. These include adrenergic, muscarinic and opioid receptors. Activation of a GPCR allows interaction with a G-protein, which is composed of α, β and γ subunits. Activated Gα subunits then interact with an effector molecule to produce a second messenger, which then brings about a cellular response (Table 3). Activated Gα subunits can also interact with ion channels to modulate ion conductance.

Drug-receptor interaction

As noted above, drug receptor interaction can generally be defined as specific, dose-related and saturable. These characteristics of a drug at a receptor are described by K_D and ED50 and can be obtained from ligand binding and dose–response curves.

The equilibrium dissociation constant K_D

The equilibrium dissociation constant K_D is loosely defined as the concentration of a radioligand that occupies half of a particular receptor population. The concentration used here is the in vitro concentration; clinically the mass (dose) of drug given to a patient is more commonly used (see below). K_D is determined experimentally and is a measure of the affinity of a drug for a receptor. More simply, the strength of the ligand–receptor interaction. To determine K_D, a fixed mass of membranes (with receptor) are incubated with increasing concentrations of a radioligand until saturation occurs. At saturation, B_max is determined (maximum receptor number) and half of this is used to determine K_D (Fig. 1). High affinity binding occurs at low drug concentrations; conversely, low affinity binding occurs at high drug concentration. If a ligand has affinity it does not necessarily mean that it will produce a response. For example, an antagonist that displays high affinity does not produce a response in its own right.

Agonists and ED50

An agonist is a drug that binds to a receptor and produces a functional response. Examples include morphine (µ-opioid receptor) and clonidine (α2-adrenoceptor). The ability to produce a response is termed efficacy (or intrinsic activity); this varies with the type of response measured. This article will consider whole animal response as much as possible. The dose range over which a response is produced is termed potency. Potency of a particular agonist can be defined from the dose–response curve (Fig. 2) as the dose of drug that produces 50% of the

Table 3 Some examples of receptor–G-protein interaction (not comprehensive)

<table>
<thead>
<tr>
<th>Receptor</th>
<th>G-protein</th>
<th>Effector/2nd messenger(s)</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid/α2-adrenergic</td>
<td>G_i</td>
<td>Adenylyl cyclase, cAMP, VSCC, Ca^2+, K^+</td>
<td>Reduced NT</td>
</tr>
<tr>
<td>β2-Adrenergic</td>
<td>G_s</td>
<td>Adenylyl cyclase, cAMP</td>
<td>Cardiac contraction</td>
</tr>
<tr>
<td>α1-Adrenergic</td>
<td>G_q</td>
<td>Phospholipase C, IP3/DAG</td>
<td>Vascular contraction</td>
</tr>
</tbody>
</table>

NT = neurotransmission; VSCC = voltage sensitive Ca^2+ channels; K_m = inwardly rectifying K^+ channel; IP3 = inositol(1,4,5)triphosphate; DAG = diacylglycerol.

Fig. 1 Saturation binding experiment. As the concentration of radiolabel increases the amount bound increases until saturation (B_max). At half B_max the K_D is extrapolated. This rectangular hyperbola is often converted to a semi-logarithmic plot from which more accurate estimates can be obtained. In this example the K_D is estimated at 1 nM (1 × 10^-9 M) or as a pK_D (−log K_D) of 9.

Fig. 2 Dose–response curve illustrating the characteristics of agonists. Full and equipotent partial and high potency partial agonists are shown. Potency is the dose range over which a response is produced and described by ED50. In this example, the ED50 for the full and equipotent partial agonist (point 1 on the graph) is 300 ng and for the high potency partial agonist (point 2 on the graph) is 10 ng. Efficacy or the ability to produce a response for the partial agonist is lower than for the full agonist. In this example the rank order of efficacy is full > high potency partial > equipotent partial.
maximum response (ED\textsubscript{50}); the maximum response itself is a crude
measure of efficacy.

It is important to remember that potency and efficacy are
different concepts and cannot be interchanged. If an agonist
has high efficacy, it does not necessarily mean that it will display
high potency and vice versa. An agonist that produces the max-
imum response capable in that system is termed a full agonist and
anything producing a lower response is a partial agonist. These
principles are illustrated in Figure 2. The full agonist is shown in
closed squares. In this example, the efficacy is 100\% and potency
(ED\textsubscript{50}) is 300 ng [midway between 100 ng (10\textsuperscript{-7} g) and 1 mg
(10\textsuperscript{-6} g) on a log scale]. In filled circles is an equipotent (same
ED\textsubscript{50}) partial agonist of lower efficacy (maximum response
\textsim 40\%). However, in the open circles a low efficacy high
potency (ED\textsubscript{50} = 10 ng) partial agonist is shown. Again, note
that in this example, potency and efficacy are not interchangeable.

How do potency and efficacy relate to affinity? As noted
previously, just because a ligand has affinity it does not necessarily
mean that it will have efficacy; for example, a simple antagonist
will have affinity but an efficacy of zero. Clearly, for an agonist
the ability to bind to a receptor will determine the ability to pro-
duce a response and to some extent the size of that response.
However, the two are seldom linked in a linear fashion and
depend on what response is measured. Therefore, no firm defini-
tions can be given. An additional and important characteristic
of partial agonists is that they can reverse the effects of full ago-

inists. For example, a hypothetical patient given buprenorphine
(partial \mu-agonist) would require higher doses of morphine to
produce the same degree of analgesia as morphine alone
(i.e. buprenorphine will antagonize the effects of morphine at
the \mu-receptor). However, when the effects of buprenorphine
wane, morphine-induced analgesia and respiratory depression
will become more evident.

**Relationship between receptor occupation and response–receptor reserves**

If a simple receptor occupancy curve for a full agonist is plotted on
the same axes as a dose–response curve, the functional response
often lies to the left of the occupancy curve. The implication of this
is that at low receptor occupancy a full response can be produced.
It is often the case that only 5–10\% occupancy is needed to produce
a full response indicating that \textsim 90\% of receptors are not needed to
elicit a maximum response and hence form the receptor reserve.
For a partial agonist, remember that the maximum response is
reduced compared with the full agonist such that even at 100\%
occupancy a full response (similar to the full agonist) cannot be
produced. Spare receptors are not pooled or hidden; they are
simply surplus to requirements.

**Antagonists**

Neutral antagonists block the effect of an agonist. There are two
types of antagonism: competitive (reversible, surmountable)
and non-competitive (irreversible, insurmountable). For example,
naloxone is a competitive antagonists at all opioid receptors and
ketamine is a non-competitive antagonist at the NMDA-
glutamate receptor.

The action of a competitive antagonist can be overcome
by increasing the dose of the agonist (i.e. the block is surmount-
able). Both the agonist and antagonist bind to the same site on
the receptor. The effect that this has on the dose–response curve
of an agonist is to shift it to the right. As the response is
surmountable, the maximum response remains unchanged
(Fig. 3). The degree of rightward shift is related to the affinity
of the antagonist and the dose used. The higher the dose, the
more agonist needed to overcome the response. The higher the
affinity of the antagonist, the greater the shift (remember affinity
is the strength of antagonist–receptor interaction and more
agonist is needed to interrupt this interaction). Conversely, if
the degree of shift is known, then the affinity of the antagonist
can be estimated.

The actions of a non-competitive antagonist cannot be over-
come by increasing the dose of agonist (Fig. 3). This is because
the agonist and antagonist binding sites are different; hence, the
agonist will not displace the antagonist molecule (e.g. ketamine
binds in the NMDA receptor channel pore but the agonist,
glutamate, binds to the extracellular surface of the receptor).
Graphically, the actions of an irreversible antagonist are the
same as those for a non-competitive antagonist but the

![Fig. 3 Dose–response curve illustrating the characteristics of antagonists. A competitive antagonist shifts the agonist dose response curve to the right with no change in the apparent maximum response obtained. The non-competitive or irreversible antagonist depresses the maximum response.](http://ceaccp.oxfordjournals.org/)

Continuing Education in Anaesthesia, Critical Care & Pain | Volume 4 Number 6 2004 | 183
explanation is different; for the irreversible antagonist the binding site may be the same as the agonist but as it is irreversible (often chemically linked) it cannot be displaced and hence cannot be overcome.

**Mixed agonists–antagonists**

Where subtypes of receptors occur, it is possible that a single ligand can have agonist and antagonist properties (i.e. mixed pharmacology). Some of the best illustrations of this occur in opioid receptors of which there are three classical subtypes: \( \mu \), \( \delta \) and \( \kappa \). For example, pentazocine is an antagonist at \( \mu \) and an agonist at \( \delta/\kappa \) opioid receptors.

**Inverse agonists**

In the receptor definition above it was stated that ‘in the unbound state a receptor is functionally silent’ and this is true in most cases. However, some receptor systems display constitutive activity, either experimentally as a result of over expression or as a result of mutation. These receptors are active in the absence of agonist. An inverse agonist would inhibit this constitutive activity and, as such, is said to display negative efficacy. Figure 4 illustrates this principle where a conventional agonist, a competitive antagonist and an inverse agonist are displayed. The actions of both the agonist and inverse agonist can be reversed by a competitive antagonist as described above. The clinical significance of inverse agonism remains to be explored but inverse agonism has been reported for several systems including benzodiazepine and cannabinoid receptors.

**Fig. 4** Dose–response curve illustrating the characteristics of an inverse agonist. In this example a negative efficacy of \(-50\%\) is shown. An agonist and antagonist are included for comparison.

**Key references**


See multiple choice questions 133–135.