

## The Question Concerning Technology, and Other Essays (Harper Perennial Modern Thought)

With very few exceptions, in order for a drug to affect the function of a cell, an interaction at the molecular level must occur between the drug and some target component of the cell. In most cases the interaction consists of a loose, reversible binding of the drug molecule, although some drugs can form strong chemical bonds with their target sites, resulting in long-lasting effects. Three types of target molecules can be distinguished: (1) receptors, (2) macromolecules that have specific cellular functions, such as enzymes, transport molecules, and nucleic acids, and (3) membrane lipids.

Receptors are protein molecules that recognize and respond to the body's own (endogenous) chemical messengers, such as hormones or neurotransmitters. Drug molecules may combine with receptors to initiate a series of physiological and biochemical changes. Receptor-mediated drug effects involve two distinct processes: binding, which is the formation of the drug-receptor complex, and receptor activation, which moderates the effect. The term affinity describes the tendency of a drug to bind to a receptor; efficacy (sometimes called intrinsic activity) describes the ability of the drug-receptor complex to produce a physiological response. Together, the affinity and the efficacy of a drug determine its potency.

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Differences in efficacy determine whether a drug that binds to a receptor is classified as an agonist or as an antagonist. A drug whose efficacy and affinity are sufficient for it to be able to bind to a receptor and affect cell function is an agonist. A drug with the affinity to bind to a receptor but without the efficacy to elicit a response is an antagonist. After binding to a receptor, an antagonist can block the effect of an agonist.

The degree of binding of a drug to a receptor can be measured directly by the use of radioactively labeled drugs or inferred indirectly from measurements of the biological effects of agonists and antagonists. Such measurements have shown that the following reaction generally obeys the law of mass action in its simplest form:  $\text{drug} + \text{receptor} \rightleftharpoons \text{drug-receptor complex}$ . Thus, there is a relationship between the concentration of a drug and the amount of drug-receptor complex formed.

The structure-activity relationship describes the connection between chemical structure and biological effect. Such a relationship explains the efficacies of various drugs and has led to the development of newer drugs with specific mechanisms of action. The contribution of the British pharmacologist Sir James Black to this field led to the development, first, of drugs that selectively block the effects of epinephrine and norepinephrine on the heart (beta blockers, or beta-adrenergic blocking agents) and, second, of drugs that block the effect of histamine on the stomach (H<sub>2</sub>-blocking agents), both of which are of major therapeutic importance.

Receptors for many hormones and neurotransmitters have been isolated and

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biochemically characterized. All these receptors are proteins, and most are incorporated into the cell membrane in such a way that the binding region faces the exterior of the cell. This allows the endogenous chemicals freer access to the cell. Receptors for steroid hormones (e.g., hydrocortisones and estrogens) differ in being located in the cell nucleus and therefore being accessible only to molecules that can enter the cell across the membrane.

Once the drug has bound to the receptor, certain intermediate processes must take place before the drug effect is measurable. Various mechanisms are known to be involved in the processes between receptor activation and the cellular response (also called receptor-effector coupling). Among the most important ones are the following: (1) direct control of ion channels in the cell membrane, (2) regulation of cellular activity by way of intracellular chemical signals, such as cyclic adenosine 3',5'-monophosphate (cAMP), inositol phosphates, or calcium ions, and (3) regulation of gene expression.

In the first type of mechanism, the ion channel is part of the same protein complex as the receptor, and no biochemical intermediates are involved. Receptor activation briefly opens the transmembrane ion channel, and the resulting flow of ions across the membrane causes a change in the transmembrane potential of the cell that leads to the initiation or inhibition of electrical impulses. Such mechanisms are common for neurotransmitters that act very rapidly. Examples include the receptors for acetylcholine and for other fast excitatory or inhibitory transmitter substances in the nervous system, such as glutamate and gamma-aminobutyric acid (GABA).

In the second mechanism, chemical reactions that take place within the cell trigger a series of responses. The receptor may control calcium influx through the outer cell membrane, thereby altering the concentration of free calcium ions within the cell, or it may control the catalytic activity of one or more membrane-bound enzymes. One of these enzymes is adenylate cyclase, which catalyzes the conversion of adenosine triphosphate (ATP) within the cell to cAMP, which in turn binds to and activates intracellular enzymes that catalyze the attachment of phosphate groups to other functional proteins; these may be involved in a wide variety of intracellular processes, such as muscle contraction, cell division, and membrane permeability to ions. A second receptor-controlled enzyme is phosphodiesterase, which catalyzes the cleavage of a membrane phospholipid, phosphatidylinositol, releasing the intracellular messenger inositol triphosphate. This substance in turn releases calcium from intracellular stores, thus raising the free calcium ion concentration. Regulation of the concentration of free calcium ions is important because,

like cAMP, calcium ions control many cellular functions. (For more information on intracellular signaling molecules, see second messenger and kinase.)

In the third type of mechanism, which is peculiar to steroid hormones and related drugs, the steroid binds to a receptor that consists primarily of nuclear proteins. Because this interaction occurs inside the cell, agonists for this receptor must be able to cross the cell membrane. The drug-receptor complex acts on specific regions of the genetic material deoxyribonucleic acid (DNA) in the cell nucleus, resulting in an increased rate of synthesis for some proteins and a decreased rate for others. Steroids generally act much more slowly (hours to days) than agents that act by either of the two other mechanisms.

Many receptor-mediated events show the phenomenon of desensitization, which means that continued or repeated administration of a drug produces a progressively smaller effect. Among the complex mechanisms involved are conversion of the receptors to a refractory (unresponsive) state in the presence of an agonist, so that activation cannot occur, or the removal of receptors from the cell membrane (down-regulation) after prolonged exposure to an agonist. Desensitization is a reversible process, although it can take hours or days for receptors to recover after down-regulation. The converse process (up-regulation) occurs in some instances when receptor antagonists are administered. These adaptive responses are undoubtedly important when drugs are given over a period of time, and they may account partly for the phenomenon of tolerance (an increase in the dose needed to produce a given effect) that occurs in the therapeutic use of some drugs.

## Reference

[Encyclopedia of Electronic Components Volume 2: LEDs, LCDs, Audio, Thyristors, Digital Logic, and Amplification](#)

[Remote Engineering Management: Managing an Engineering Team in a Remote-First World](#)