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Conventional Drugs: How do they work?

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Background

One way conventional medicine differs from traditional or complementary medical practice is in its rapid, extensive and immediate exploitation of technological advances. This applies not only in diagnostic procedures and emergency treatment, but in the extensive application of drugs and other patented pharmaceutical products. These are now universally used in the management of acute disorders, in chronic and recurring conditions, in the prevention of numerous disorders, and in the enhancement of normal, everyday functions. Indeed, there are very few disorders or conditions for which the first line of orthodox therapy does not involve the use of one or more drugs. Moreover, many drugs are now used as prophylactic or protective agents in the alleviation of a number of chronic disorders which are related to dysfunctional or inadequate lifestyles.

In most countries, conventional drugs dominate the medical treatment of virtually all physical and mental conditions, and even numerous social disorders.

The scientific study of drugs is *pharmacology.* It deals with the physical properties of natural, semi-synthetic and new-to-nature agents which have an effect on the body; particularly the ways they interact with the many physiological systems. The discipline is relatively young, probably emerging at the turn of the 19th century. This is when Paul Erhlich described the search for the magic bullet, a selectively toxic synthetic chemical which would cure syphilis, but leave the sufferer unscathed.

Drugs act in complex ways, many of which are still not completely understood. Generally, the drug's action is to either stimulate or depress certain biochemical and physiological functions within the body. A drug may act generally upon all cells within the person's body, as with chemotherapy. Conversely, another drug may pinpoint only certain cells or tissues, or a particular organ. Different drugs act in different locations. One may exert its action on the surface of the cell, another on structures within the cell. Yet another may act on a key enzyme in a biochemical sequence within the body. However, all drugs do have one characteristic in common – *they act on structures called* ***receptors.***

Drugs mimic certain body substances such as hormones and neurotransmitters.

What is a receptor?

A receptor is a highly specialised protein , embedded in the membrane of a living cell. It is a dynamic part of the cell's structure, under tight regulation both from the inside by numerous intracellular chemicals, and from the outside by various extracellular controlling factors. The receptor receives specific chemical signals from far and wide: from other cells close by or from more distant endocrine glands. These signals stimulate the cell into carrying out some specific, pre-determined action. This could be, for example, to secrete a hormone, or synthesise an enzyme.

Substances which bind to specific receptors are known as *ligands.* These come in a wide variety of sizes and shapes. Some may be simple chemicals, like *thyroxin*, *adrenaline* or *acetyl choline*; others are small proteins like peptides, such as *cytokines*; yet others are protein hormones, like *growth hormone*. Ligands are not only substances produced by the body: *toxins*, derived from plant, pathogenic bacteria or even some species of animal, will also stimulate particular receptors (causing perhaps a catastrophic reaction).

Most drugs are ligands. They target specific receptors in the body and produce an effect characteristic of the tissue in which the receptor is located.

Every cell has a large number of receptors on its surface membrane or internal structures. Also, each cell surface has several different types of receptors, depending on the type and function of the cell. Much of the body's normal activity is regulated by receptors, which respond in a unique fashion to stimuli from specific ligands. Every receptor is highly selective regarding the ligand it will bind to.

The cell and its membrane

The cell is the basic unit of all living matter. This is the *fundamental physical unit of life* which is capable of independent existence. Most individual cells are so small they are invisible to the naked eye, and can only be seen using a microscope. A few, such as the hen's egg, are easily seen. In the human body, there are around *100 trillion cells*. Most of these contain a *nucleus* which is surrounded by the *nuclear membrane.* Most of the cell's volume is made up of a viscous, jelly-like substance, the *cytoplasm*.

Cells contain a wide variety of *inorganic* chemicals such as water, and *electrolytes* like sodium, calcium, chloride and phosphate. But there are other chemicals characteristic of life which are known as *organic substances*. These can be big – like *proteins* and *nucleic acids*; or small, like *amino acids* and *fatty acids*. The large ones are called *macromolecules*, which are often structural components of cellular organelles.

Cells also contain numerous specialised sub-cellular structures, called *organelles*. These include the *mitochondria (*which supplies energy for the cell*), the endoplasmic reticulum (*the cell's internal transport system*), lysosomes (*which destroy alien substances like bacteria*), Golgi apparatus* (which store newly synthesised proteins*),* and *ribosomes (*where proteins are synthesised*).*

Drug action usually starts at the *cell (*or *plasma) membrane.* This is a thin layer of cells which encloses a cell. A similar type of structure also encloses organs and individual tissues. Also, there are membranes *within* cells, enclosing the various organelles (mentioned above).

The membrane itself is made up mainly of *phospholipid* molecules, which are double layers of complex lipids arranged so that the outside layer is *hydrophilic* ("water loving") and the inner layer *hydrophobic* ("water hating"). The hydrophilic head contains phosphorus groups, and faces outwards. The hydrophobic tail, made up of fatty acids, faces inwards. There are also some *proteins* embedded in the cell membrane. The cell membrane is therefore described as a *lipoprotein* structure. The membranes have several roles: they help maintain the structure of the cell; they make up the enzymes which different cell surfaces possess; and they are also an essential part of drug receptors.

The cell membrane is* semi-permeable*. It lets water, ions and small neutral molecules like sugar pass through. Electrically charged particles or large molecules like proteins cannot.

Another important function is to separate the different cell compartments, and also isolate the interior of the cell from the outside environment. Even at high magnification, they all have a similar appearance: a double two-dimensional sheet, separated by a narrow space.

Categories of drugs

There are three basic categories of drugs: *agonists, antagonists,* and *partial agonists*.

Agonists. If a drug prompts the protein receptor to respond in the same way as the naturally occurring hormone or neurotransmitter does, then the drug is referred to as an *agonist.* Agonists are ligands which stimulate the body's cells, tissues or organs into producing a specific response or effect. An agonist will act on, or *bind to*, a receptor, and so trigger a sequence of events in the cell. This ultimately results in an increase or decrease of a particular cell activity. Examples of natural, or *endogenous*, agonists are acetyl choline, histamine and nor-adrenaline. A number of drugs fall into the agonist category –the bronchodilators used to treat bronchial asthma, for example, belong to a class of *beta-agonists*. Some drugs used to treat Parkinson's disease symptoms are called *dopamine agonists*. They stimulate dopamine receptors, which are deficient in the disease.

A number of herbal products contain agonists, such as ginger, valerian, turmeric, and ginkgo biloba.

Antagonists have the opposite effect. They are drugs which interact with receptors by effectively blocking them, but do not cause any observed effect. In effect, they deny access of the natural agonist at the receptor site, reducing its effect. They actually bind to the receptor, but do not stimulate it. Receptor antagonists can be classified either as reversible or irreversible. Reversible antagonists attach to the receptor, but readily break away (*dissociate*) from it. The irreversible antagonist, however, forms a stable chemical bond with the receptor. Many drugs have antagonist actions. They include the alpha and beta blockers used in various cardiovascular disorders, the dopamine antagonists used in treating psychoses, and the serotonin antagonists prescribed for treating depression.

Several herbal products contain antagonists, such as saw palmetto, chamomile and Nigella sativa. Also, the caffeine in tea and coffee.

Partial agonists are ligands which act as antagonists at low or medium dose levels, but display some agonist activity at high doses.

Agonist	**Partial agonist**	**Antagonist**
High affinity & high efficacy	*High affinity & low efficacy*	*High affinity & no efficacy*
Rapid turnover of ligand at receptor site	*Medium turnover with ligand at receptor site*	*Low turnover of ligand at receptor site*

Drugs are usually grouped according to their *desired action*. If they are used to lower blood lipids, they are termed *lipid-lowering agents*. If their desired action is to lift depression, they are known as *anti-depressants*. Similarly, *anti-hypertensive agents* are used for treating abnormally high blood pressure, *anxiolytics* for relieving anxiety, *bronchodilators* for easing breathing problems caused by narrowing of the bronchi, and

Drugs and receptors

Drugs work by stimulating or blocking specialised receptors which are located either on cell membranes or on particular regions of enzymes. In doing so, they influence or regulate the rate of specific chemical reactions within the cells affected.

The reason a drug produces an effect, whether it is stimulation or inhibition, is that structurally it is similar to a naturally active ligand at the molecular level. At the molecular level, it has a 3-dimensional shape (or *configuration*) which is very similar to the active site of the hormone or other natural substance. The drug interacts with specific structures which are themselves the targets of the naturally occurring substance. These receptors are already present for regular cellular activities, as they are connected to other cell structures which carry out the cell's many functions. When the cell's receptors are stimulated (or inhibited), cellular function is modified.

There are two important terms which describe the interaction of the drug with its receptor – *affinity* and *efficacy*. *Affinity* refers to the binding capacity of the drug to the receptor, and is based on the time a drug adheres to the receptor site. *Efficacy* refers to the degree to which the drug stimulates the target receptor. Another term employed is *turnover* – this is a measure of the coming and going of ligands at the receptor's active site.

A drug will have an effect on a particular cell or tissue *only* if there are receptors on the cell membrane which recognise the drug. Once the drug has positively identified its specific receptor site, it will bind to it in a *reversible* way – that is, not stick to the receptor permanently. The drug will then initiate its particular pharmacological effect.

A model for a drug-receptor action is the lock and key. The key may enter and open the lock (agonist); or it may enter, but not turn (antagonist).

The drug will compete with natural active agents for *occupancy* of the receptor site. This competition will result in the site being occupied by the drug if there is *more* of the drug in the vicinity, or by the active ligand if there are *more* of these around. For example, a beta blocker will compete with nor-adrenaline at an adrenergic receptor site. If there are large numbers of the beta blocker molecules around, due to the patient taking a high dose of the drug, the receptor sites will be mainly (but not totally) occupied by the beta blocker molecules. So the receptor site will be blocked, and unable to fully carry out its natural activities. Conversely, if there is a majority of nor-adrenaline molecules close to the receptor site, the beta blocker will have little opportunity to get to and block the sites, so its pharmacological impact will be diminished. This is the basis for the *dose-response phenomenon*, where the greater the dose of the drug, the greater the impact, until all the receptor sites have been occupied. When this occurs, increasing the drug dose will not increase the tissue response.

Drugs cannot cause the target tissue or organ to do something it is not capable of doing normally.

Drug specificity

The drug itself must have a specific molecular shape, or *spatial configuration*. The drug must be *receptor specific*. So whether a drug will have an effect on a particular and/or tissue is determined by the presence

the cell surface, will determine the extent to which the drug has an effect. Another factor which dictates the intensity of the drug's biological effect is the actual concentration of drug molecules at the receptor site

Few if any drugs demonstrate absolute specificity. This means that a drug may stimulate one type of receptor to a predominant degree, but the drug will still have a minor (but often significant) effect on another type of receptor. For example, a drug which possesses histamine receptor blocking ability often blocks cholinergic receptors to some extent. That is, the antihistamine drug is able to block histamine receptors effectively, but not 100%. There is also a small but finite blocking effect on cholinergic receptors too. In practice, this type of antihistamine will reduce the histamine-related allergic symptoms, but also cause anticholinergic adverse drug reactions, such as drowsiness, blurred vision and dry mouth.

Most birds can eat red-hot peppers with impunity. Why? Because they do not have receptors for capsaicin, the hot ingredient present in the vegetable.

Similarly, one drug may stimulate a particular receptor site in one particular tissue in the body, but not have a major effect on the same receptor types in another tissue in the body. For example, the newer beta blockers will stimulate beta adrenergic receptors in the heart and blood vessels, but not in the lung. The advantage of this is that breathing problems do not develop with this particular beta blocker.

Operation of the receptor

In the day-to-day, drug-free situation, the body's cells are continually exposed to a wide variety of hormones, nutrients, chemical messengers and other *endogenous* (internally produced) substances which are present in the blood, lymph or interstitial cellular fluid bathing the tissues. These act directly on their specific receptors, and in doing so bring about a reaction from the tissue which adjusts the body to a changing environment, either internal or external. In this way, the body's metabolism is closely regulated, and homeostasis maintained.

There are several steps between the ligand appearing at the receptor site, in this case a conventional drug, and the final response to the drug by the tissue affected.

Step 1. The drug which interacts with the receptor is called the *first messenger*. This initial interaction between the drug and its specific receptor leads to a signal being transmitted to an *intermediate structure* within the cell's interior.

Step 2. This intermediate substance is a specialised protein, called a *G-protein*. The G-protein actually belongs to a family of proteins which transmits signals received from hormones and other endogenous agents. The receptor and G-protein are connected, or *coupled*. When a signal is received by a G-protein from a receptor, then an event occurs in the cell.

Step 3. The G-protein regulates and controls a particular cell function. One important function is to bring about a rise in the level of *calcium ions* within the cell. It can fine-tune this aspect of cellular activity, by switching it on or off. One important action that is triggered by the receptor-G-protein complex is the formation of another key compound, *cyclic AMP* (cyclic adenosine mono-phosphate).

Step 4. Calcium ions combine with cyclic AMP, resulting in the formation of the *second messenger*. This takes the signal transmission process further, so that the cell responds to receptor stimulation by carrying out its 'core function'. For example, it may be to absorb a nutrient, if the cell is in the digestive tract; or to contract, if it is a muscle cell; or to secrete a hormone, if the cell is in an endocrine gland.

The second messenger is not always cyclic AMP. It can be a similar substance, cyclic GMP. It can also be a protein, calmodulin, or a prostaglandin.

Step 5. The second messenger interacts with a number of enzymes, collectively termed *protein kinases*. These ubiquitous enzymes act by adding an *energy-rich phosphate* group to one or more molecules which are responsible for the affected cell's particular function. By adding the phosphate group to the molecule, it changes its shape (a process termed *configuration*), which results in increased biological activity.

Step 6. The final response varies according to the cell's role in the body. If it is a muscle cell, then it will contract; if an endocrine cell, it will secrete a hormone; if it is a bone cell, it will influence bone formation.

Step 7. Once the cell has carried out the appropriate response, the drug, which is bound reversibly at the receptor site, will detach. It may do this spontaneously, or be displaced by another ligand which seeks to occupy the binding site. The cell's activity will return to its normal resting level.

One interesting feature of receptors is their capacity to *self-regulate*. If there is an urgent requirement to restore internal homeostasis, the number of receptors for particular endogenous ligands can be increased in number (*up-regulated*) or decreased in number (*down-regulated*). This feedback mechanism allows for better fine-tuning of the body's metabolic activities. It also explains why the activity of certain drugs begins to wear off when they have been given for some time.

Drug interaction at receptors

The effects of one drug at a particular receptor may be interfered with by the simultaneous intake of another drug. The result is usually a reduction in the effect of one or both drugs. These unwanted or unexpected drug interactions explain why a patient may fail to respond to drug therapy. They may also be the reason for side effects, or *adverse drug reactions*. Therapeutically, drug interactions may in fact be the desired interaction, as with multi-drug therapy of hypertension, asthma, or infections, for example. In these situations the interaction may provide a *synergistic action*; that is, the combined effect is greater than the sum of the two individual parts

Types of receptors

The body's possesses a wide range of tissues, and each contains many different types of receptors. Different tissues have different profiles of receptors, according to their function in the body. Muscle cells have a preponderance of one type of receptor, and endocrine glands have a preponderance of another.

A neurotransmitter is a ligand released from nerve endings which initiates a nerve impulse to another nerve, muscle or endocrine cell.

A receptor is classified according to the endogenous ligand which normally binds to it. A small selection of well-documented receptors is tabulated below, together with their bodily function:

Type of receptor	Endogenous ligand	Biological effect
Adenosine receptor	*adenosine*	Responsible for dilation of the bronchioles & blood vessels
Adrenergic receptor	*Adrenaline, nor-adrenaline*	Major player in the fight or flight response
GABA receptor	*gamma amino butyric acid*	An inhibitory neurotransmitter Involved in sleep and vigilance
Cholinergic receptor	*acetyl choline*	Part of the parasympathetic nervous system
Dopamine receptor	*dopamine*	Involved in voluntary body movement and reward systems
Histamine receptor	*histamine*	The main mediator of the allergic and anaphylactic reaction
Opioid receptor	*endorphins*	Involved in pain relief, and coughing and vomiting actions
Angiotensin receptor	*angiotensin II*	Part of the blood pressure regulating system
Glucagon receptor	*glucagon*	With insulin, is responsible for glucose regulation
5-HT receptor	*Serotonin*	Many roles in mood, appetite, blood vessel constriction

There are many more, and new ones are being discovered almost on a regular basis.

Drug action via enzyme inhibition

Instead of attaching to receptors located on cell membranes, some drugs target *enzymes.* An enzyme is a protein produced in the body which increases the rate of biological reactions. It is present in small amounts, and is not affected by, or used up in, the reaction it catalyses. The enzyme acts by binding to the substance it is catalysing (the *substrate*) at a specific zone on the enzyme, and converting it into a different substance (the *product*). There are several thousand different types of enzymes involved in the myriad metabolic processes occurring in all biological systems. Each enzyme is (relatively) specific for a certain reaction. There are, for example, enzymes which act only to hydrolyse substances (the *hydrolases*), or add a phosphate group to some other substance (the *phosphorylases*), or catalyse the breakdown of proteins (the *proteases*), and so on.

Examples of drugs that target enzymes are: ACE-inhibitors, cox-2 inhibitors, protease inhibitors and aspirin,

Enzymes are an essential part of virtually all biological systems. For instance, the maintenance of a person's blood pressure within narrow limits is mediated extensively by enzymes, as is the inflammatory reaction. So interfering with one or more enzymes in a sequence of enzymatic reactions can help correct a metabolic disturbance. This *enzyme inhibition* effect is capitalised upon by numerous drugs.

An enzyme inhibitor attaches to the active site which is located on the enzyme molecule, and so reduces its activity by blocking it off physically. In the body, there are numerous natural enzyme inhibitors. These act to maintain homeostasis, regulate the cell's metabolic pathways, and also prevent any enzymatic activity which may damage the cells.

Many natural enzyme inhibitors exist in the body. Their role is to regulate metabolism.

Several major drugs act as enzyme inhibitors. For example, the ACE inhibitors, which are used to lower raised blood pressure, act upon *angiotensin converting enzyme (ACE*). This is part of a complex sequence of interconnected enzymatic reactions which lead ultimately to the synthesis of angiotensin II. This substance is a very active natural blood vessel constrictor, so reducing the amount produced will lead to a fall in peripheral resistance and so lower blood pressure.

There are several such drugs which act on specific enzymes, and a selection of these is summarised in the table below:

Drug	**Enzyme targetted**	**Pharmacological effect**
ACE inhibitors (e.g. Renetec)	*Angiotensin converting enzyme*	Reduces AT-2 formation, BP lowered
Aspirin	*Prostaglandin synthetase*	Analgesic, antipyretic, anti-inflammatory
Statins (e.g. Lipitor)	*HMG co-enzyme A transferase*	Reduced synthesis of cholesterol
MAO oxidase inhibitors	*Mono amine oxidase*	Depression relieved
Terbinafine (e.g. Lamisil)	*Squalene epoxidase*	Skin fungal infections eliminated
COX-2 inhibitors (e.g. Celebrex)	*Cyclo-oxygenase*	Inflammatory flare ups diminished
Anti-retroviral agents	*HIV proteases*	Opposes the viruses in HIV/Aids
Penicillin and derivatives	*DD transpeptidase*	Stops or kills pathogenic bacteria

The enzyme is inhibited when the drug occupies the active site, so preventing the natural substrate from reaching it. In the case of drugs, this binding is competitive; that is, as more substrate accumulates at the active site, the drug is displaced, and

Many plant-derived poisons act as inhibitors of key enzymes. This property deters predators.

normal activity resumes. The drug does not change the active site permanently, but merely distorts the amino acid configuration in the active site, preventing access of the natural substrate.

Two parameters have been adopted to describe the pharmacological competence of a drug acting as an enzyme inhibitor. First, there is the *potency*. This is a measure of how much of the drug is needed to inhibit the enzyme to a certain degree (usually 50%). Second, there is *specificity*. This indicates the degree to which the drug acts only on the enzyme's active site, and not on other sites on the enzyme.

Summary

The scientific study of conventional drugs is pharmacology. Conventional drugs act by interfering with receptors. These are protein structures fixed in tissue, which normally respond to hormones, neurotransmitters or other chemicals. There are many different types on the body, with each type responsible for a specific action. Different cells and tissues have different complements of receptors, according to their role in the body. Conventional drugs work by attaching to receptors in the cells of living tissue. As a result, some biochemical or physiological action is either stimulated or inhibited, depending on whether the drug is an agonist or antagonist. Some receptors are located on a section of certain enzymes, which themselves are protein in nature, and a number of drugs act by interfering with enzyme function by binding to these regions. The action of drugs at receptors is complex, consisting of a number of discrete steps involving different cellular processes, such as the second messenger and G-proteins.

Further reading

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