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RESEARCH ARTICLE

THE PHARMACOLOGY OF WESTERN DRUGS

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ABSTRACT

Western pharmacology is a relatively new scientific discipline, having originated around 150 years ago. It can be divided into two broad categories: pharmacodynamics (the effect drugs have on the body) and pharmacokinetics (the effect the body has upon the drug). This review is concerned with the former: the way drugs exert their pharmacological action. The keystone of Western pharmacology is based on the Receptor Theory, where the drug acts as a "key" to undo a "lock in specific parts of the body". The receptor is a membrane-located macromolecule with both binding and activity sites. The pharmaceutical drug attaches to the binding site, and either stimulates (as an agonist) or blocks (as an antagonist) the receptor, initiating or inhibiting the receptor's dedicated action. Some drugs (partial agonists) combine both effects. Receptors are normally acted upon by natural ligands, such as hormones, neurotransmitters, and growth factors. Receptors, of which there are many types, are spread throughout the body's tissues, and in the case of antimicrobial agents, within viruses and bacteria. Receptors are also present in ligand ion channels, where they are involved in nerve transmission and hormone secretion.

INTRODUCTION

Most present-day conventional medicine practice revolves around the use of pharmaceutical products – prescription drugs – for the treatment of a broad range of acute, chronic, and recurring disorders (Goodman & Gilman, 2014). These drugs are also extensively used by practitioners of Integrative Medicine (Bhikha et al, 2008; Blom, 2003). It is therefore imperative to understand how they work in practice, what their side effects are and why they occur, and if and how they interfere with the action of herbal remedies (Cupp,1999). One question is whether the action of the drug interferes with the body's natural ability for self-healing. Are the innate mechanisms for healing pushed to one side by the action of specific drugs used in particular ailments? In many cases the answer must be "yes". Suppressing particular symptoms, such as vomiting, fever, coughing, and inflammation may inhibit the potent forces underpinning self-healing and protection against cancer and infection (Bhikha & Haq, 2000). The pharmacological and toxicological actions of most modern drugs are complex physical and chemical processes, in many cases not completely understood (*Limbird, 2004); Colquhoun, 2006).*However, the net effect of most is to either stimulate or depress certain biochemical and physiological functions within the body. The drug may act generally (systemically) upon all cells within the body, as chemotherapeutic agents do.

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Alternatively, the drug may take effect locally in certain cells or tissues, or even on a complete internal organ, as a beta blocker does. Furthermore, the drug may exert its action on the surface of the cell, or on membranes or structures within the cell. It may also act within an organ to inhibit a key enzyme in a biochemical cascade which is essential for regulatory or metabolic performance. It may also interfere with the operation of ion channels, as calcium channel blockers and proton pump inhibitors do (Prull, 2006). In this article "conventional drugs" refers to any artificial chemicals, whether based on new chemical entities or on naturally occurring substances, which are used as a medicine to treat troublesome disorders, prevent disease, or help diagnose it. They are usually available from the pharmacist or via prescriptions.

Historical insight

Western pharmacology is a broad science of the properties of chemicals and drugs and their interactive effects on the body's biological systems (structure, function, and properties) to cure disease or alleviate symptoms (Dorland's Medical Dictionary). Early pharmacological studies revealed that minute amounts of specific substances could have extensive effects on the body's physiological systems, and slight changes in the chemical structure of the substance would result in radically different responses. The structure of the cell responsible for the effect was termed *the receptor* (*Ahlquist, 1948).* This was viewed as a biological switch, activated or blocked by specific chemicals.

Early pioneers of pharmacology were Wohler, who synthesised urea, Magendie, who in 1809 reported the effect of strychnine on dogs, and Claude Bernard, who in 1842 described the pharmacological action of curare at the neuromuscular junction (Maehle,1999). The first universities to study pharmacology were in Dorpat, present-day Estonia (1847) and Michigan, USA (1890). Schmiedeburg, a student of another pioneer, Buchheim, is now regarded as the true founder of Western pharmacology, publishing the first scientific text, "Outline of Pharmacology" in 1878. Abel researched adrenaline, histamine, and insulin during the period 1897 to 1926, and his student Reid Hunt discovered acetyl choline in 1906. Erhlich (1854–1915) described the search for the "magic bullet", a selectively toxic synthetic chemical which would cure syphilis and leave the sufferer unscathed. (Silverstein, 2002; Prull, 2003). Langley (1852–1926) introduced the concept of the drug receptor, visualising it as a switching mechanism which could be turned off and on by specific drugs. From this time onwards, many pharmacologists in various countries, such as Dale (1875-1968) (Dale,1943), Loewi (1873-1961), and Ahlquist were involved in the rapid progress of Western pharmacology.

Two different approaches to disease

Two distinguishing features between conventional medicine and complementary medical practice are the exploitation of advanced technology, especially in the fields of diagnostics and emergency treatment, and the extensive reliance on patented pharmaceutical products, especially drugs, in the management of both acute and chronic recurring medical conditions. There are few disorders for which the first line of conventional therapy does not involve the use of drugs. The use of powerful drugs as prophylactic or protective measures in the alleviation of chronic disorders, many related to persistently poor lifestyles, is now becoming established conventional medical practice. The risks posed by raised blood pressure, glucose and cholesterol levels, gastric secretion, and tissue inflammation is now routinely addressed by specific conventional drugs.

Conventional medicine views the body as a physical machine whose parts and systems must be adjusted or replaced regularly due to wear and tear or disease (Bhikha, 2000). The receptor theory fits nicely into this model (Berkow & Fletcher, 1992). Good health happens when the machine (and its plethora of receptors) is working properly; disease occurs when a specific part of the machine (or some of its receptors) malfunctions. The idea of drugs fits into this model, as they restore proper working order to discrete parts of the body-as-machine, keeping the internal systems functional, at least until the next malfunction. Perhaps the main objection to conventional drugs raised by exponents of complementary or traditional medicine is that they largely suppress symptoms, but do not actually bring about a cure for the ailment (with the possible exception of anti-bacterials). Although this usually is a satisfactory response when treating acute symptoms such as headache, inflammation, and breathing difficulties, and signs such as fever, high blood pressure and cholesterol, it does little or nothing to eliminate the underlying cause(s) of the symptoms. On the other hand, the naturalistic view, shared by Tibb, Ayurveda, and Naturopathy, adopts a different concept of health and disease. It regards health as the dynamic equilibrium, maintained by inner healing, which exists between the person, the lifestyle followed, and the environment. In this model, disease reflects a disturbance in this harmony, which leads to a range of signs and symptoms. Many diseases, whether heart disease, depression, cancer, or rheumatism, are caused to a greater or lesser extent by a faulty lifestyle. Tibb considers that Nature itself provides the remedies needed to achieve physical and emotional wellbeing. Tibb and other forms of naturalistic medicine are highly respectful of the innate healing powers of the human body, and focus on natural ways for restoring inner harmony. Much of the treatment of ailments and the maintenance of good health, revolve around measures calculated to support and stimulate inner healing. First, the troubling symptoms are dealt with, then the underlying causes are sought, identified, and neutralised.

The nature of a receptor

Much of the body's normal activity is regulated by *receptors*, which respond to stimuli from specific *ligands,* resulting in a physiological response (*Kenakin,2004).*. A receptor is a glycoprotein molecule embedded in a living cell's membrane surface, with a unique 3-dimensional structure. It is a dynamic part of the cell's structure, under tight regulation both from the inside (*intracellular*) by numerous substances, and from the outside (*extracellular*) by a number of circulating hormones and other controlling factors. Every cell has a large but finite number of receptors, with several different types built into its surface membrane (Limbird, 2005). The receptor receives specific chemical signals from other nearby cells, or from more distant tissues. These signals stimulate the cell into performing some specific action. This could be to let other substances enter the cell, or to reproduce, or to secrete, a specific hormone. Substances which bind to specific receptors are known as *ligands (*Petrucci, 2007). These come in a variety of chemical forms, sizes, and geometric shapes. Some may be simple, naturally occurring chemicals, such as *thyroxin*, *adrenaline, or acetyl choline*, others are small proteins such as peptides or *cytokines* and *interferons*. Others are larger protein hormones such as *growth hormone* and *ACTH*. They target specific receptors in the body and elicit a predictable and reproducible effect.

Ligands are not restricted to substances produced in and by the body. Pharmaceutical drugs, whether synthetic or derived from natural substances, are also classed as ligands. *Toxins*, derived from plant, pathogenic bacteria, or even some species of animal, will also stimulate particular receptors, sometimes precipitating a catastrophic reaction. Each receptor is highly selective regarding which ligand it binds to; it must possess a high affinity for this particular ligand at the levels normally found in the body. *Intrinsic efficacy* is a measure of the ligand's strength (whether natural substance or synthetic drug) to bind to the receptor. The effect by the ligand on the total receptor stimulus is proportional to the number of receptors occupied.

Working of the receptor

In the day-to-day, drug-free situation, the body's cells are continually exposed to a variety of hormones, nutrients, chemical messengers, and other *endogenous* (internally produced) substances present in the blood, lymph, or interstitial cellular fluid bathing the tissues.

List of tables

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

Type of receptor	Endogenous agent	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, 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

Drug	Enzyme inhibited	Pharmacological effect
Aspirin	*Prostaglandin synthetase*	Analgesic, antipyretic, anti-inflammatory
Statins	*HMG co-enzyme A transferase*	Reduced synthesis of cholesterol
MAO oxidase inhibitors	*Mono amine oxidase*	Depression relieved
Terbinafine	*Squalene epoxidase*	Skin fungal infections eliminated
COX-2 Inhibitors	*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
Theophylline	*Phosphodiesterase*	Bronchodilator used in asthma

Pharmaceutical agent	Ion channel involved	Clinical outcome
Nifedipine	Calcium ion channels	Anti-hypertensive, vasodilatation
Verapamil	Calcium ion channels	Anti-arrhytmic, anti-angina
Phenytoin	Sodium ion channels	Prevention of epilepsy
Lamotrigine	Sodium and calcium ion channels	Anti-convulsant
Lidocaine	Sodium ion channels	Anaesthetic
Benzodiazepines	Chloride ion channels	Migraine prophylaxis
Pregabalin	Calcium ion channels	Muscle relaxant, analgesic
Omeprazole, pantoprazole	Proton and sodium ion channels	Anti-secretory, anti-ulcer

Bacterial target	Condition	Antibiotic
Cell walls	Gram-positive infections	Penicillins, cephalosporins, vancomycin
Cell membranes	Gram-negative infections	Polymyxins, polyenes
Protein synthesis	Both Gram types	Tetracyclines, aminoglycosides, erythromycin
Nucleic acids	Gram-negative infections	Rifampin, quinolines
Metabolism	TB, other lung infections	Sulfa drugs, isoniazid

Antiviral agent	Clinical condition	Mode of action
Amantadine	Influenza	Blocks release of viral RNA and uncoating
Acyclovir	Genital herpes, shingles, chickenpox	Inhibits viral DNA synthesis
Idoxuridine	Eye herpes	Inhibits viral DNA replication
Zidovudine	HIV/Aids, Aids-related complex	Inhibits viral reverse transcriptase
Ribavirin	Influenza, resp.syn. virus, Lassa fever	Prevents viral RNA and DNA synthesis
Interferons	Hepatitis A and C	Encourage immune system to destroy virus
Stem-navirs	HIV/Aids, hepatitis C	Inhibit viral protease

These act directly on their specific receptors, like a key activating a lock. The key may enter the keyhole and open the lock (acting as an agonist), or it may enter the lock but not turn it, and prevent other keys from doing so (antagonist) (Ross and Kenakin, 2001). In doing so, they elicit a reaction from the tissue which rapidly adjusts the body to a changing internal or external environment. In this way, the body's metabolism is closely regulated, and the body's homeostasis (internal dynamic harmony) is maintained.

Several steps take place between the drug appearing at the receptor site and the final response to the drug

Step 1.A drug entering the body and reaching the tissues is defined as a *first messenger*. The 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. The intermediate substance is a specialised protein, a *G-protein*. The G-protein belongs to a family of proteins which transmits signals received at the receptor from hormones and other endogenous agents. The receptor and G-protein combine, an event termed *coupling*. This results in an event characteristic of the receptor.

Step 3. The G-protein regulates and controls a particular cell function. One important function is to bring about a rise in the concentration of *calcium ions* within the cell. It can turn this aspect of cellular activity on or off, or amplify or modulate it.

One important action that is triggered by the receptor-G-protein complex is the formation of the key compound *cyclic AMP* (cyclic adenosine mono-phosphate).

Step 4. The combination of calcium ions with cyclic AMP results in the formation of the *second messenger*. This agent takes the signal transmission process further, so that the cell responds to receptor stimulation by carrying out its "core function". This may be to absorb a nutrient if the cell is part of the digestive tract, or to contract if it is a muscle cell, to secrete a hormone if the cell is present in endocrine tissue, or to form new bone if it is present in osteoblastic bone cells.

Step 5. The mechanism for achieving this usually involves interacting 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. 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 second messenger is usually cyclic AMP. Different cells utilise other forms of the second messenger, such as *cyclic guanosine mono-phosphate* (cGMP), a dedicated protein called *calmodulin*, or certain *prostaglandins*. One interesting feature of receptors is their capacity to *self-regulate*. According to the requirements for internal homeostasis, the number of receptors which identify and bind with particular hormones or other endogenous ligands can be increased (*up-regulated*) or decreased (*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, a common phenomenon termed *tachyphylaxis.* Following stimulation of the surface receptor, certain other cells may change the synthesis or release of a particular endogenous substance – an enzyme, or hormone, or neurotransmitter, for example. The type of cell which adopts this process often acts as a stimulus or signal to other cells.

The cell membrane

The cell is the basic structural and functional unit of all living matter. It is the *fundamental physical unit of life* that is capable of independent existence. Most individual cells are so small they can only be seen using a microscope. A few, such as the hen's egg, can be seen unaided. Cells contain a wide variety of *inorganic* substances, many of which are found in the inanimate world, such as water, and *electrolytes* such as sodium, calcium, chloride, and phosphate. There are also *organic* substances that are more characteristic of life. These can be large macromolecules, such as *proteins* and *nucleic acids*, or small, such as *amino acids* and *fatty acids*. The large ones are often structural components of cellular organelles. In the human body, there are around *100 trillion cells*. Most of these contain a *nucleus* surrounded by the *nuclear membrane.* Most of the cell's volume is made up of a viscous, jelly-like substance, the *cytoplasm*. Cells also contain other specialised structures, called *organelles*. These include the *mitochondria (*supplying energy for the cell*), the endoplasmic reticulum (*the cell's internal transport system*), lysosomes (*which dissolve alien substances entering the cell, such as bacteria*), Golgi apparatus (*storage sites for newly synthesised proteins*),* and *ribosomes (*sites in the cell where proteins are synthesised*).*

There are several features of a cell which distinguish it from non-living material:

- ***Metabolism* –** the ability to break down nutrients and from them produce energy, create new cells, and replace defective or redundant cellular structures.
- ***Homeostasis* –** the ability to maintain equilibrium within the internal environment.
- ***Growth* –** the ability to increase in size and repair itself.
- ***Responsiveness* –** the ability to react to internal and external stimuli.
- ***Reproduction* –** the ability to divide and multiply, creating other cells.
- ***Information* –** keep the environment, internal and external, informed of situation.

The membrane is made up mainly of *phospholipid* molecules, double layers of complex lipids arranged so that the outside layer is *hydrophilic* ("water loving") and the inner layer *hydrophobic* ("water hating").There are also some *proteins* embedded in the cell membrane. These have several roles: they help maintain the structure of the cell and make up the enzymes that different cells possess. They are also an essential part of drug receptors. The cell membrane is therefore described as a *lipoprotein* structure. The phospholipid molecules are lined up so that the *hydrophilic* head containing the phosphorus group faces outwards, and the *hydrophobic* tail, made up of fatty acids, faces inwards. The cell membrane separates the different cellular compartments and isolates 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. The cell membrane is *semi-permeable* – it allows the passage across of water, ions, and small electrically neutral molecules such as sugar, but not electrically charged particles or large molecules such as proteins. Drug action usually starts at the *cell membrane*. Sometimes called the *plasma membrane*, this is a thin layer of tissue enclosing a cell. The same structure also encloses organs and individual tissues. There are also membranes within cells enclosing the various organelles within the cell, such as the nucleus, mitochondria, and secretion granules.

Categories of drugs

In the pharmacological arena, there are three basic categories of drugs: *agonists, antagonists,* and *partial agonists*. Agonists are ligands which bind to and stimulate the body's cells, tissues, or organs into producing a specific response or effect. (Black & Leff, 1983). An agonist binds reversibly to, i.e. has affinity for, a receptor. This stimulates the receptor into triggering a sequence of events culminating in a change in one aspect of a cell's activity (either increasing or decreasing it). Examples of natural, or *endogenous*, agonists are *acetyl choline, histamine,* and *nor-adrenaline*. Many 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. Antagonists have the opposite effect: they will bind reversibly to their receptors, but do not stimulate them. Their impact is to deny access of naturally occurring agonists such as hormones and neurotransmitters by *blocking* the receptor site. By doing so, they prevent their action. No response ensues. Many prescription drugs are antagonists: *beta blockers* for hypertension, *dopamine antagonists* for psychosis, *serotonin antagonists* for migraine, for example.

Partial agonists are ligands which act as antagonists at low or medium dose levels, but display some agonist activity at high doses. Examples are *methyl-dopa*, used to treat Parkinson's Disease, the beta blocker acebutalol, and the synthetic estrogens *tamoxifen* and *clomiphene*. Overall, drugs can be described in terms of their binding capacity, or *affinity,* with the receptor. This term actually refers to the length of time that a drug occupies its particular receptor site. The extent to which a drug stimulates its target receptor is described by the term *efficacy.* They can also be described in terms of their *turnover,* which is a measure of the coming and going of ligands at the receptor's active site.

The reason a drug produces an effect, whether stimulation or inhibition, is that at the molecular level it is structurally similar to a naturally active ligand that normally occurs in the body. It has a 3-dimensional shape (or *configuration*), similar to the active site of the natural active substance. As such it interacts with specific receptors located on cells and tissues, the targets of the naturally occurring substance. The receptors are already present for regular cellular activities and they are connected to other cell structures that carry out the cell's many functions in response to biochemical signals from the receptors. When the cell's receptors are stimulated (or inhibited), cellular function is modified. In Western pharmacology practice, drugs are 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 *anti-secretory* agents for gastric distress from excessive stomach acid secretion.

Drugs and receptors

A drug will have an effect on a particular cell or tissue *only* if there are receptors on the cell membrane which are recognisable to the drug. Drugs cannot cause the target tissue or organ to do something it is not capable of doing normally. Once the drug has positively identified its specific receptor site, it binds to it in a *reversible* way –it does not stick to the receptor permanently. The drug will then initiate, or *signal*, its particular pharmacological effect. The drug will compete with natural active agents for *occupancy* of the receptor site. This competition results at the site being occupied by the drug if there is *more* of the drug in the vicinity, or by the natural active ligand if there are more of these around. For example, a beta blocker will compete with nor-adrenaline (*nor-epinephrine*) at adrenergic receptor sites. 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 effectively blocked, and unable to fully carry out its normal activities under the influence of nor-adrenaline. 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 site, 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.

Drug specificity

The drug itself must have a specific molecular shape, or *spatial configuration*. The drug must be *receptor specific*. So whether a drug has an effect on a particular tissue is determined by whether suitable receptors are present or absent. Furthermore, the *receptor density,* or number of receptors per unit area of the cell surface, will determine the extent to which the drug has an effect. Another factor dictating 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 will also 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. 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. Similarly, one drug may stimulate particular receptors in one particular body tissue, but not have a major effect on the same receptor types in another body tissue. For example, the newer beta blockers will stimulate beta adrenergic receptors in the heart and blood vessels, but not those located in the lung.

Types of receptors

The body's extensive range of tissues contains many different types of receptors. Different tissues have different profiles of receptors, according to their function in the body. Muscle fibre cells have a preponderance of one type of receptor, and endocrine glands have a preponderance of another type. Receptors are classified according to the transmitter chemical agent which normally binds to them. A small selection of well-documented receptors, together with their bodily function is included in the List of tables: There are many more, and new ones are being identified on a regular basis. The biochemistry of the body is turning out to be vastly more complex than previously thought.

Drug interaction at receptors

All pharmaceutical drugs have one feature in common: they act on structures called receptors. So the possibility of one drug interfering with another drug at a receptor is real and common. The effects of one drug are often affected by the simultaneous intake of a different drug of similar 3-D structure. The result is frequently a reduction of the effect of one of the drugs. Unwanted drug interactions are often the

origin of failure to respond to drug therapy. They may also result in side effects, or *adverse drug reactions*. In contrast, there may be an enhanced effect. Therapeutically, drug interactions may be the desired interaction, as with multi-drug therapy of, for example, hypertension, asthma, or infections. In these situations the interaction may provide a *synergistic action*: the combined effect is greater than the sum of the two individual parts.

Drug action via enzyme inhibition

Enzymes are an essential part of virtually all biological regulatory systems. An enzyme is a protein produced in the body that 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.

Many natural enzyme inhibitors exist in the body. These act to maintain homeostasis, regulate the cell's metabolic pathways, and prevent any enzymatic activity which may be damaging the cell. For instance, the maintenance of a person's blood pressure within narrow limits is mediated extensively by enzymes, as is blood clotting and the inflammatory reaction. So interfering with one or more enzymes in a sequence of enzymatic reactions can help correct a metabolic disturbance. Many plant-derived poisons act as inhibitors of key enzymes. This property deters predators. An enzyme inhibitor attaches to the active site located on the enzyme molecule, and reduces its activity by blocking it off physically. 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 leads ultimately to the synthesis of angiotensin II. This substance is an active natural blood vessel constrictor, so reducing the amount produced will lead to a fall in blood pressure.

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

With pharmaceutical drugs, enzyme inhibition is *competitive*; as more substrate accumulates at the active site, the drug is displaced from the active site, and normal activity resumes. In other words, the drug does not change the active site permanently, but merely distorts the amino acid configuration of the active site. Two parameters have been adopted to describe the pharmacological competence of a drug acting as an enzyme inhibitor. First is *potency*. This is a measure of how much of the drug is needed to inhibit the enzyme to a certain degree (usually 50%). Second 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.

Drug interaction channels

Certain drugs (and several toxins) act at ion channel receptors, which convert chemical signals into electrical impulses in so-called excitable tissues such as neurons and muscle. They are made up of complex proteins arranged in bundles forming a passageway (*pore*) through the cellular membrane, where ions such as calcium, potassium, and sodium rapidly pass when the pore opens. Different ion channels are specific for certain ions; only potassium ions can pass through potassium channels, for instance. Ion channels open and close in response to substances which stimulate or block receptors located at the ion channel.

There are two basic types of ion channel:

- *Voltage-gated channels*, stimulated by changes in voltage across the cellular membrane, and involve sodium, potassium, and calcium.
- *Ligand-gated channels*, stimulated by neurotransmitters such as GABA, acetyl choline, glycine, and many others.

These channels are essential for nerve transmission. They are therefore firmly implicated in the onset of several common neurological disorders such as Parkinson's disease, migraine, and epilepsy, in certain psychiatric conditions such as psychosis and ataxia, in disorders with a marked neurological component such as multiple sclerosis, cardiac arrhythmia, and certain forms of hypertension. Numerous drugs are known to act on receptors at ion channels. A selection of these, together with their target clinical effect, is given in the list of table.

Anti-microbial drugs

Pharmaceutical agents which attack hostile microbes, or *pathogens*, that have become established in the living body, impede their growth in different ways. This is done until the body's defense mechanisms are capable of completing the removal of the remaining microbes. *Antibiotics* interfere with a number of aspects of bacterial growth or replication. Different antibiotics differ in their target sites of action, whether it is (a) cell wall synthesis, (b) cell membrane activity, (c) protein synthesis, or (d) DNA synthesis or replicationsee List of tables. *Antiviral agents*are relatively few in number, as the Western clinical approach to viral infections has largely been based on vaccines. They do not generally eliminate the offending virus, but inhibit their replication.The available anti-viral agents are summarised in the List of tables.~~below:~~Most commonly used *antifungal agents* are the azoles, which act on the fungal cell membrane by interfering with the metabolic sequence of enzymes, which results in the synthesis of *ergosterol*, an essential steroid analogous to mammalian cholesterol. There are two basic groups of azoles: the *imidazoles*, such as *ketoconazole,clotrimazole*and*miconazole*, which possess broad activity against most pathogenic fungi such as the dermatophytes, and the *triazoles*, such as *fluconazole* and *itraconazole*, which are effective for Candida infections.

Summary

A drug is any organic physical substance which is used legally to treat the symptoms of a disease, or to prevent the disease from occurring. It can be natural in origin, or synthetic or

semi-synthetic. It acts upon the body to alter the rate at which a particular function of the body occurs. Western pharmacology is based upon the receptor theory, which is analogous to the action of a key (the drug) on a lock (the receptor). Receptors, which are located on cellular and sub-cellular membranes, are normally stimulated or inhibited by natural ligands such as neurotransmitters and hormones, but can be affected by specific pharmaceutical drugs. Some drugs (agonists) act to stimulate the receptors, whereas others (antagonists) act to inhibit them. A third category (partial agonists) blocks the receptor to some extent, but does possess some intrinsic stimulant activity. The receptor is made up at the molecular level by a binding site and an activity site. Both have to be occupied for a conformational change to occur prior to any pharmacological action taking place. The ligand or drug binds reversibly to the receptor by a reversible ionic force. Receptor activation involves drug/ligand interaction, release of the G-protein, involvement of calcium ions, formation of the second messenger, protein kinases, and finally a typical physiological response. The physiological response to these agents is proportional to their concentration at the membrane receptor site, and to the efficiency with which the cell converts the stimulus into a response. Some drugs act to block ion channels in cell membranes, preventing nerve transmission or hormone secretion. Antibiotics act in diverse ways to interfere with the metabolism of the target microbes, especially in cell wall synthesis or activities of the nucleus. Anti-viral agents interfere with replication of the viral genetic replication apparatus and functioning.

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