

AN INTRODUCTION TO PHARMACOLOGY

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Summary

Broadly defined, pharmacology is the study of the actions of chemicals on the body and most usually it is defined as chemicals that can have a therapeutic action to treat disease. Since it looks at the interaction between chemicals and body systems pharmacology utilizes the basic disciplines of chemistry, biochemistry, physiology, pathology and microbiology in its practice. Pharmacology is a foundation science for pharmacy which is the rational prescribing of drugs to treat disease and the foundation science for toxicology which is the study of the toxic actions of chemicals on the body. Pharmacological methodology in understanding chemical action is relevant for many areas of therapeutics including herbal medicines, Chinese medicine, natural products, as well as chemicals, therapeutic drugs and socially used drugs. Pharmacologic methodology serves to describe how a drug acts in the body and in many cases the scientific studies of drug action were instrumental in developing an understanding of body function in health and disease. Many of the fundamental discoveries in medical science were made as scientists sought to find explanations to explain drug action in the body. The divide between pharmacology and physiology is esoteric with many of the early pioneers of medicine being claimed by both disciplines as key contributors. In the Pharmacology theme whilst there is an organization on the basis of therapeutic area, there are also topics to define the basic scientific principles of pharmacology. The theme is not a resource for

therapeutic prescribing and the reader is directed to more precise prescribing information such as in the many national formularies (e.g. the Australian Medicines Handbook, British National Formulary; United States Pharmacopeia and National Formulary; World Health Organisation Model Formulary). Comprehensive textbooks include: Rang and Dale's Pharmacology; Goodman and Gilman's The Pharmacological Basis of Therapeutics; Basic and Clinical Pharmacology.

1. History of Pharmacology

From the beginnings of time, pharmacology has had a place in human history in all cultures. The initial primitive pharmacology knowledge developed from experiences on which plants when eaten were safe and which were toxic. In such a fashion a catalogue of good and bad evolved and was passed down through oral traditions. This was transformed over time to include natural sources which appeared to cure or ameliorate disease. In our earliest written histories descriptions of therapeutic natural products exist. In the Ebers papyrus, written in Egypt in the 16th century BCE, beer, turpentine, myrrh, juniper berries and poppy and other therapies were described to treat disease. Similar historical records exist for most ancient civilizations including the Sumerian, Indian and Chinese.

There are many threads back into antiquity and the book History of Medicine by Lois Magner is a wonderful treatise describing the evolution of medicine and therapeutics. One thread that is easily followed is that of opium, which even today is the source of key modern day pain killers and exemplifies the evolution of pharmacology. The story starts with the Sumerians around 3400 BCE who cultivated the opium poppy in lower Mesopotamia and recorded its actions in clay tablets. It was referred to as the "joy plant" and its reputation led to its spread across neighboring civilizations such as Egypt. Around 460 BCE Hippocrates, a famous Greek physician and teacher of medicine, described opium as having narcotic properties and also described opium use in treating internal diseases. Both Roman and Greek physicians did much to spread knowledge of opium's medical use. Even then, the addictive properties of opium were clear, properties which were to be implicated in serious social problems across the world which are evident even today.

In 330 BCE, Alexander the Great introduced opium to Persia and India and by the year 400 it had reached China. In the 10th century, the noted Islamic physician Avicenna of Persia described opium as "the most powerful of stupeficients". About the year 1200 ancient Indian medical treatises *The Shodal Gadanigrah* and *Sharangdhar Samahita* describe the use of opium for diarrhea and sexual debility. In the 1300's opium disappeared from European historical record and it was not until 1527 that opium was reintroduced into European medical literature by Paracelsus as laudanum which was prescribed as a painkiller.

The modern era began in 1680 when the English apothecary, Thomas Sydenham, introduced Sydenham's Laudanum which became prototypical for many opium proprietary brands and was used for numerous ailments. In 1803, the German Friedrich Sertürner dissolved opium in acid then neutralized it with ammonia. The result was morphine which, in contrast to raw opium, exhibited long-lasting and predictable effects. By 1827 morphine was in commercial manufacture. In 1874, English researcher, C.R. Wright synthesized heroin which went into commercial production in Germany in 1898. More recently, opioids and derivatives with a range of pharmacokinetic properties produce more effective control of pain.

The molecular basis of opioid action unraveled after Solomon Snyder and Candace Pert located the molecular site of action and discovered specific proteins which were activated by opioids in 1972. These opioid receptors were found in neural tissue and mediate the pain reducing effect. It was reasoned that if the receptors exist that they may form part of a physiological pathway. John Hughes

and Hans Kosterlitz then discovered that humans produce endogenous morphine-like compounds, the enkephalins, which act on opioid receptors. Endorphins, which are human peptides also were discovered and also activate opioid receptors.

The history of opioids above hint at two important pharmacological concepts the first is the ability to alter the duration of the effect as exemplified by the development of morphine and the second is the existence of receptors which transduce the biological action. These effects embed the concepts of pharmacokinetics and pharmacodynamics.

Whilst the theme Pharmacology could encompass natural products and the use of herbal and remedies, it is restricted here to contemporary drugs and medicines except where the natural remedies have found themselves in current contemporary clinical use. An exception is the discussion of venoms, poisons and toxins. The story of pharmacology is an evolution from the historic herbal traditions of many cultures through to definition of active principles and refinement of action based on chemical synthesis and a strong understanding of physiology and protein structure. The pharmacology story is played at many levels but has as its underpinning the definition of pharmacology as a science with theories and principles discovered and accepted by rigorous investigation. Thus pharmacodynamics, molecular pharmacology and pharmacokinetics serve to define drug action and predict useful therapies for the future.

2. Pharmacodynamics and Receptors

Receptors play a key role in the history of pharmacology particularly during its 20th century history. Whilst we now know the molecular identity of receptors (see section on molecular pharmacology below), initial discussions on describing the physical sites of drug action in the body as receptors was a theoretical treatise pioneered by John Langley and Paul Ehrlich. The receptor concept gained strength and the discipline of pharmacodynamics evolved as a quantitative science of drug receptor interactions. Even though the physical identity of receptors was unknown at this time, the effects of drugs on organ and cell responses could be observed. The effect of drug concentrations on responses and interactions between drugs were quantified by mathematical formulas. There were many pioneers including A.J Clark in the 1930s, and later E.J Ariens and R.P Stephenson in the 1950s. Drugs not only activated receptors but could also act as antagonists and the development of the classic theory of drug antagonism was pioneered by Gaddum, Schild and Arunlakshana. These were the beginnings of quantitative pharmacodynamics which is the study of the interaction of the drug molecule with receptors. Pharmacology history has seen the evolution of the receptor concept from an abstract idea to defined physical targets which consist of enzymes, ion channels, proteins, DNA, nuclear structures and specialized membrane protein receptors. This latter class contains the superfamily of G-protein coupled receptors (GPCR's) which recognizes the widest variety of hormones and chemical transmitters.

Pharmacodynamic principles are a set of tools to define and measure the affinity (its ability to bind) that a drug has for a receptor and its ability to induce the receptor to produce a response in the cell/tissue (efficacy). The definitions underpin modern pharmacology. The term agonist refers to a molecule that produces a response through a receptor and efficacy is the property of a molecule that causes the receptor to induce a biological effect in the host cell. Antagonism is the binding of a molecule to a pharmacological receptor to render that receptor unable to respond to agonists. Antagonism can be orthosteric where drugs compete for the same binding site or allosteric where the receptor has different binding sites for the agonist and antagonist and the interaction between these alters the receptor and the effect of the agonist.

Affinity of the drug for a receptor is a measure of how well a drug binds to a receptor and can be calculated by a variety of means e.g. by examining the binding of a radioactive drug to the receptor

and competition for the binding by a non-radioactive drug. Efficacy describes how well a drug activates a receptor once it is bound to the receptor. Affinity and efficacy may be separately affected by chemical structure of the drug. Thus a high affinity/low efficacy compound is possible and many of these are effective antagonists. Many of these concepts yielded sophisticated models which were used to classify, test and predict drug action.

Orthosteric drug antagonism is where both agonist and antagonist compete for the same site and is often referred to as competitive antagonism. In some circumstances true competition does not occur because the antagonist dissociation from the receptor is slow and in some cases irreversible. Where antagonism is truly competitive Schild regression can describe the level of antagonism and also can determine whether the antagonism is truly competitive. Allosteric modulation can either increase or decrease drug action depending on the nature of the conformational change in the receptor protein and is not competitive. Where antagonism is observed, allosteric modulation is saturable. Partial agonism is the case where the ligand has a low efficacy and produces a positive response but when tested with an agonist of higher efficacy decreases the action of that agonist because it competes for the same receptor site.

Receptors are thought of as existing in several states with inactive and active conformational forms. An inverse agonist is a ligand that has preferential affinity for the inactive form. If the active receptor produces a basal response without the need for a stimulatory agonist then the inverse agonist will depress this by preventing transition into the active form. These concepts have underpinned drug discovery through the rational quantitative description of drug effects and in particular drug potency as determined by affinity and efficacy measures as well as antagonist potency.

3. Molecular Pharmacology

Pharmacodynamics described that action of drugs in systems and it was only later that the molecular pathways by which drugs acted were discovered. Drugs in the main interact with proteins to produce a biological effect and the principal targets are receptors, enzymes, transport molecules and ion channels. Molecular pharmacology is the study of the molecular pathways that are altered by drugs within the body to produce an effect. In the various topics within this theme of pharmacology, molecular pathways involved in drug action are described in the context of each therapeutic area. A useful review is: Alexander et al., (2008), Guide to Receptors and Channels, which lists the receptors channels and molecular signaling and structural information. To help the reader the section below is a brief summary of the main molecular concepts in drug action.

3.1. Receptors: Ligand Gated Ion Channels

Ligand gated ion channels are multi subunit proteins which form transmembrane ion channels and the opening can be initiated and modulated by drugs and transmitters binding to specific domains on the channel allowing the passage of ions such as Na^+ , Ca^{2+} and K^+ . In the main they mediate fast events such as neuronal synaptic transmission. Examples include nicotinic acetylcholine receptors, γ -aminobutyric acid GABA_A receptors, glycine receptors, serotonin 5HT_3 receptors, glutamate receptors (AMPA, Kainate, NMDA) and P_{2x} purinoceptors for ATP. The nicotinic acetylcholine receptor for example consists of 5 subunits which span the cell membrane and form an ion pore. Acetylcholine binds to the outer areas of one of the subunits to increase channel opening and allow Na^+ flow along its concentration gradient into the cell. The cellular response is a net current causing either depolarization, hyperpolarization or Ca^{2+} entry. There are no molecular steps in ligand gating as it is a direct interaction of the drug with the receptor and a fast event. Receptor states such as inactive, desensitized and active represent different conformational states. Inhibitors of ligand binding can act as channel inhibitors. For example, tubocurarine blocks the binding of acetylcholine

to its binding site on the nicotinic acetylcholine receptor and hence causes muscle paralysis. It should be noted however that there are non-ligand dependent drug actions at ligand gated ion channels including blockade of the channel pore and allosteric modulation by agonists and antagonists.

3.2. Receptors: G-protein Coupled Receptors

G-protein coupled receptors (GPCRs) are the largest family of receptors representing the sites of action of many hormones and transmitters and are the most common target for therapeutic drugs. Typical examples of GPCRs include receptors for adenosine, acetylcholine (muscarinic only), adrenaline, angiotensin II, bradykinin, calcitonin, dopamine, endothelin, follicle-stimulating hormone, γ -aminobutyric acid (GABA), glutamate (metabotropic only), histamine, neuropeptide Y, leukotrienes, noradrenaline, opioids, oxytocin, platelet-activating factor, prostaglandins, serotonin, somatostatin, tachykinins and vasopressin. There are many intracellular signaling pathways modulated by GPCRs including Cyclic AMP / Protein Kinase-A pathway, Ca^{2+} / (Protein Kinase- C) pathways, Phospholipase- C pathways, Protein Tyrosine Kinase pathways, PKC/MEK (MAPK/ERK1) pathway, p43/p44MAPK (Mitogen Activated Protein Kinase) pathway, p38 MAP pathway, PI3K (Phosphoinositide-3 Kinase) pathway, NO-cGMP pathway, Rho pathway, NF-KappaB (Nuclear Factor-Kappa B) pathway and others.

A GPCR consists of a single peptide which, traverses the cell membrane 7 times and is coupled to GTP binding proteins (G-proteins) intracellularly. G proteins are heterotrimeric proteins containing α -, β - and γ subunits that are present in the internal side of cell membranes. In the inactive state, α -subunit is bound with GDP. Receptor activation results in GTP binding to the α -subunit in the place of GDP and dissociation of the α subunit from the $\beta\gamma$ complex allowing the separated α -subunits to activate downstream pathways. There are multiple types of G proteins (G_i , G_o , G_s etc) which have diverse actions. Currently there are at least 20 known α subunits, 6 β subunits, and 11 γ subunits. An intrinsic GTP'ase activity of the α -subunit, converts the GTP back to GDP and the complex reforms.

There are many examples of GPCR signaling. For example in the case of β -adrenoceptors, the α -subunit of G_s stimulates the production of cAMP from ATP by stimulating the membrane-associated enzyme adenylate cyclase. cAMP acts as a second messenger that goes on to activate protein kinase A (PKA). PKA phosphorylates many different downstream targets to alter cell function. This underlies for example β -adrenoceptor stimulation of heart rate. On the other hand, receptors linked to G_i inhibit the production of cAMP from ATP by inhibiting adenylate cyclase. Another example is the α_1 -adrenoceptor which is linked to $G_{\alpha q/11}$, the α -subunit of which stimulates membrane-bound phospholipase C beta, which then cleaves phosphoinositol biphosphate (a minor membrane phosphoinositol) into two second messengers, inositol trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 releases Ca^{2+} from intracellular stores and DAG activates the protein kinase C family of enzymes which has a diverse range of intracellular targets such as receptors, ion channels, enzymes and structural proteins involved in neural activity, smooth muscle contraction and gene activation amongst others. In the case of α_1 -adrenoceptors, this signaling contributes to constriction of smooth muscle as an example.

Whilst the majority of G protein actions are exerted through the α subunit, the $\beta\gamma$ complex sometimes also has active functions such as the opening of K^+ channels in the heart by muscarinic acetylcholine receptors and coupling of some receptors to L type Ca^{2+} channels. In these cases second messenger molecules are not involved in the signaling.

In addition to the heterotrimeric G proteins linked to receptors, there are other GTP binding proteins. For example, Rho is a family of small GTPase proteins which control a wide variety of

cellular processes including: actin cytoskeleton organization; cell growth, proliferation, differentiation, production of reactive oxygen species (ROS). In contrast to the heterotrimeric G proteins linked to receptors, Rho is not directly activated through ligand binding to G protein-coupled receptors (GPCRs). The activation/inactivation of Rho-GTPase is modulated by integrated internal signaling as well as extracellular signaling from GPCRs for example thrombin receptors in platelets.

New research indicates that GPCRs can assemble as multimeric complexes and in some cases are constitutively active without an external ligand. Further, the signaling pathway linked to a receptor may in some cases alter depending on which activated state is produced by a ligand.

It was recognized early on in the development of receptor theory that receptor activation often produced a desensitization whereby subsequent activation of a receptor was less effective in producing a response. Indeed, this explains in part the tolerance that develops to opioids for example. At the molecular level it is clear that receptors are tightly regulated and regulation can occur via inhibition of GPCR/G-Protein coupling, trafficking of receptors between the cell membrane and cytosol and receptor degradation. GRKs (G-protein-coupled receptor kinases) and arrestins regulate these processes. GRKs specifically phosphorylate the activated form of the receptor, which in turn promotes arrestin binding which inhibits coupling of the GPCR to its G protein and targets the receptor for internalization. Thus either internalization or decreased coupling of the receptor to its G protein explains functional desensitization.

3.2. Enzyme Linked Membrane Receptors

The general feature of enzyme linked membrane receptors is that they have an extracellular domain which can be activated by ligands. This domain is directly linked to an enzyme active domain located intracellularly. In some cases ligand activation leads to dimerization a process of two subunits associating with one another. This then produces active enzymic activity. The basic model is that the ligand induces dimerization of the receptor and transphosphorylation of tyrosine residues in the cytoplasmic domain. This phosphorylated domain is an active kinase and can either phosphorylate or interact with intracellular proteins to initiate signaling cascades many of which alter gene transcription and therefore later cell growth and differentiation. These are the tyrosine kinase receptors. Examples include insulin and many growth factors such as epidermal growth factor. In some cases such as for transforming growth factor the kinase is selective for serine threonine residues. Cytokine receptors are a variation of this model that lack intrinsic enzyme activity but rather they assemble from subunits and bind to and activate intracellular kinases such as Jak upon ligand activation. Finally some enzyme linked membrane receptors have intracellular guanylate cyclase activity. An example is the receptor for atrial natriuretic factor which generates cyclic GMP which in turn activates protein kinase G family to initiate a large range of signaling cascades. It should be noted that there exists a soluble guanylate cyclase which is structurally different and is activated by nitric oxide to generate cyclic GMP.

3.4. Nuclear Receptor Family

These receptor targets are intracellular receptors which in some way initiate changes in gene transcription upon activation. Some are cytoplasmic which form homodimers on activation and then translocate to the nucleus after activation and activate response elements to activate genes. Examples of this type of receptor include the steroid receptors such as the glucocorticoid receptors and the sex steroid receptors such as those for estrogen and testosterone. Some nuclear receptors are already present in the nucleus and these in general are activated by lipid ligands and also act by modulating gene transcription.

3.5. Ion Channels

Whilst receptors can influence ion channels through signaling pathways including G-proteins and direct ligand gating (see above), ion channels can also transduce drug action in other ways. Drugs can act as inhibitors of ligand binding (gating) or alternatively by inhibiting ion passage through the channel pore by blocking the pore or by locking the pore in a closed state. These non-ligand/ non-receptor dependent effects represent the mechanism of action of a broad range of drugs including local anesthetics such as lidocaine, anti-dysrhythmics (anti-arrhythmics) such as quinidine, anti-convulsants such as carbamazepine and a wide variety of animal derived toxins such as conotoxins.

3.6. Molecular Basis of Bacterial Chemotherapy

Anti-infective agents are not discussed elsewhere in the Pharmacology theme and yet they are an important therapeutic area with a strong molecular basis for their mode of action. The history of antibiotics probably goes back to the ancient Egyptians, the Chinese, and Indians of Central America who all used molds to treat infected wounds. The germ theory of disease needed to be accepted before a scientific search for antibiotics commenced and this didn't occur until the late 1800s. In 1871, the surgeon Joseph Lister, observed that urine contaminated with mold did not allow the successful growth of bacteria and in the 1890's German doctors, Rudolf Emmerich and Oscar Low made pyocyanase from bacterial cultures which had limited effectiveness.

Sir Alexander Fleming observed that the bacterium *Staphylococcus aureus* could be destroyed by the mold *Penicillium notatum*, thus demonstrating antibacterial properties in 1928. But it was not until 1942 when penicillin was manufactured on a commercial scale. Fleming, Howard Florey, and Ernst Chain shared the 1945 Nobel Prize for medicine for their work on penicillin. In Germany, Prontosil, the first sulfa drug, was synthesized in 1935 by Gerhard Domagk. The 1940's and 50's heralded the discovery of a wide variety of agents mainly from natural sources that had antibacterial properties and remain today as functional antibiotics including the aminoglycosides such as streptomycin, tetracycline and nystatin.

There are several molecular pathways through which drugs act to inhibit bacterial infection. Firstly there is protein synthesis inhibition. This can occur by drugs acting at the bacterial 50S ribosome and this includes lincosamides such as lincomycin and macrolides such as erythromycin which are bacteriostatic. Drugs acting at the 30S ribosomes include the aminoglycosides such as gentamycin which inhibit protein synthesis in bacteria by irreversibly binding to the 30S ribosomal unit. This ultimately results in damage the cell membrane. Gentamycin is used in the treatment of serious Gram negative bacterial infections. The tetracyclines are bacteriostatics and also inhibit protein synthesis by reversibly binding to the 30S subunit of the ribosome.

A second pathway is the inhibition of bacterial wall synthesis and this includes the penicillins, carbapenems (e.g. ertapenam) and cephalosporins such as cefaclor which interfere with bacterial cell wall peptidoglycan synthesis. Glycopeptides such as vancomycin inhibit bacterial wall synthesis by preventing formation of peptidoglycan polymers. The penicillins interfere with bacterial cell wall peptidoglycan synthesis.

The quinolones (e.g. ciprofloxacin) are bactericidal and inhibit bacterial DNA synthesis by blocking DNA gyrase and topoisomerase IV. The rifamycins inhibit bacterial RNA polymerase. Finally bacteria have a requirement to synthesize folic acid and drugs which reduce bacterial folate biosynthesis include trimethoprim and sulfonamides

Today, antibiotic use is controversial because of the development of bacterial resistance. The widespread and inappropriate use of antibiotics has led to the natural selection of resistant strains of

bacteria which are not affected by the main drug groups. This had led in many countries to guidelines for the use of antibiotics and judicious use of the remaining few drugs to which resistance has yet to develop.

Resources and further information for antibacterial drugs as well as anti-fungal drugs, anti protozoals and anthelmintics can be found in the major formularies listed at the end of this section.

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Biographical Sketch

Professor Majewski graduated with a PhD from Melbourne University in 1979 and has had a long research career in both Germany and Australia holding many prestigious Fellowships with over of 120 publications and 21 PhD students supervised. He joined RMIT in 1999 as a departmental head and was appointed foundation Head of the School of Medical Sciences in 2001. He was responsible at RMIT for the introduction of new degrees in Biomedical and Pharmaceutical Sciences. He established the drug safety facility RDDT in 2003 and this is now a private company. He

was a member of the National Committee for Biomedical Sciences and is a former President of the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists. He is the International Editor for the Theme of Pharmacology in the UNESCO EOLSS project an online textbook for use in the Third world. His research interests are cardiovascular and neuro-pharmacology.

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