Basic concepts in pharmacology, drug action and pharmacokinetics

Part 1: Introduction to drug science: what are drugs and how do they work?

This is the first in a series of articles on the basics of pharmacology, drug action and pharmacokinetics. The topic of drug science is introduced through interactive explanations of pharmacology and its two major subdivisions, as well as brief explanations of what drugs are, how they are named, and how they produce their pharmacological effects.

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**Introduction to drug science: what are drugs and how do they work?**

Pharmacology, or drug science, is a vast and very complex science, which encompasses a wide variety of specialist study areas against a backdrop of basic sciences. These range from applied mathematics and statistical analysis, chemistry, biochemistry, genetics and physiology on the one hand, to clinical medicine, pharmacy practice and an array of associated health sciences, on the other. This article introduces some of the basic concepts that underlie pharmacology. Readers are invited to make use of the suggested activities in this series of articles to gain insight into, and to better understand, the subject matter being presented.

Drugs are chemical substances that influence physiological (including biochemical) or mental processes in the body. When used with discretion and vigilance, drugs display their beneficial biological effects in the presence of physical or mental illness. Some drugs may even be used to prevent or diagnose disease.1-3

However, the term “drug” is also associated with the use and abuse of so-called recreational substances that affect the central nervous system in one way or another, and, in so doing, cause chemical dependency or addiction.1

For the purposes of this series and for pharmacological purposes in general, the term will only be applied to drugs that are used for medicinal purposes, i.e. medicinal drugs.

**Write down your own definition of a drug:**

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____________________________________________________________________
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Drugs are the active ingredients of medicines. Therefore, drugs are pharmacologically active substances and are used in the manufacture of medication for human or animal consumption. Drugs may be used to prevent, diagnose and treat physical or mental illness, or alleviate some of the symptoms associated with such afflictions.1

New developments in the pharmaceutical industry necessitate a more modern-day definition…

Biopharmaceutical agents constitute a group of therapeutic agents that do not fit the traditional definition of drugs. In contrast to the chemical substances mentioned above, which are also referred to as small-molecule drugs or “traditional” pharmaceuticals, the biopharmaceutical agents are much larger macromolecules, produced through biotechnology as opposed to simple extraction (i.e. direct extraction from a biological source) or chemical sourcing and manufacturing (i.e. chemical synthesis).1

The use of biotechnology implies that living organisms or components such as cultured cells and tissues of such organisms, and so-called genetic engineering are involved in the manufacturing process. Biopharmaceutical agents include monoclonal antibodies, recombinant human insulin, certain vaccines, clotting factors VIII and IX, enzymes, hormones and cytokines.1
Examples include infliximab, bevacizumab, and human growth hormone (somatropin). The most common biopharmaceutical agent that pharmacist’s assistants will work with is recombinant human insulin.

Novel biopharmaceutical agents are being developed at an extraordinary pace and are already helping to shape the way in which various serious illnesses are being treated today. These include, but are by no means limited to, rheumatoid arthritis, cancer, haemophilia, ulcerative colitis and multiple sclerosis.

Note that the former term, biological agent, was originally aimed at blood products, biological poisons and all biological products used to bring about either passive or active immunity in the person receiving them, including toxoids, immunoglobulins, antitoxins and most other vaccines. The older biological agents are produced through simple or direct extraction from a biological source, hence the name, and do not involve modern-day biotechnology or genetic engineering. Examples of biological agents include equine gamma globulin, human plasma albumin, human immunoglobulin, live attenuated virus vaccines and diphtheria, tetanus and pertussis toxoid vaccines.

However, it should be noted that the term “biopharmaceutical” is also used in pharmaceutics (the art and science of drug preparation and the design of dosage forms) when referring to the so-called biopharmaceutical properties of drugs.

The biopharmaceutical properties of drugs will include all aspects related to their release, dissolution and stability. They include the ability to cross plasma membranes and other biological barriers, the resultant absorption, and the rate and extent of their presystemic elimination (i.e., their metabolism in the gastrointestinal tract and liver before they eventually reach the systemic circulation). These factors are most applicable to orally-administered drugs and will be explored in more detail in later articles.

Lately, some authors have begun to use the term “biotechnology drugs” when referring to the abovementioned biopharmaceutical agents as a more descriptive means of differentiating between the older biological agents, the novel biotechnologically-derived agents, and the biopharmaceutical properties of drugs.

Another interesting development is the advent of generic versions of biotechnology drugs. These generic biotechnology drugs are referred to as follow-on biologics (FOBs) or biosimilar agents. These biosimilar agents are considered to be similar to the innovator or branded products, but not exactly the same.

The reason for this is that the generic manufacturer (i.e., the manufacturer of the biosimilar agent) will not necessarily have access to the exact same strain of living organism or cell culture that is used by the innovator company (i.e., the manufacturer that originally discovered and developed the product).

Did you consider the following in your definition?

• Drugs are the “active ingredients” of medicines.
• Drugs fall into one of two broad categories, namely so-called small-molecule, traditional drugs (i.e., chemical agents), and large-molecule biotechnology agents.
• In this context, we are not referring to recreational drugs, street drugs or so-called abused drugs, but rather to medicines.

What is the difference between a drug and a medicine?

Drugs usually require special preparation to make them suitable for administration to patients. This may include compounding them, adding colourants, flavourings and preservatives, preparing suitable dosage forms (e.g., tablets, capsules, mixtures, elixirs and suppositories) and deciding on the most suitable dosing schedule.

The art and science of drug preparation and the design of dosage forms is known as pharmaceutics. Drugs that have been pharmaceutically prepared are called medicines. Therefore, a medicine may contain one, two or many different drugs as active substances within a suitable base of pharmaceutically inactive substances known as excipients.

Excipients: The inactive substances that are used to make up dosage forms are known as excipients. Excipients may be used as preservatives, flavourings, colourants, antioxidants, thickeners and emulsifiers. Therefore, preparing a dosage form to contain one or more active pharmaceutical ingredient(s), i.e., drugs, requires the addition of one or more excipients.

Naming drugs and medicines

What is the difference between a generic name and a trade name?
What is pharmacology?

To enable us to use and administer medicines effectively, we need to know what to expect from them and what will happen to them once they are introduced into the human body.

Write down the questions that you think a health care professional should ask/know about a medicine before prescribing, dispensing or administering it to a patient:

Why is pharmacology so important?

Pharmacology is the scientific study of drugs, where they come from, their nature, their chemical composition, their expected actions, their wanted and unwanted effects and their uses. Pharmacology has two major subdivisions, namely pharmacodynamics and pharmacokinetics.1,2,4

The two major subdivisions of pharmacology answer the two most fundamental questions that may be posed wherever drug therapy is concerned. These questions are: What will the drug do to the body? and What will the body do to the drug?

Pharmacodynamics provides us with answers to the former question, while pharmacokinetics answers the latter one.1,2,4

Pharmacodynamics describes the physiological effects that drugs have on living cells or organisms, such as the human body, and shows how drugs influence body functions through biochemical changes in body fluids and tissues. Therefore, pharmacodynamics describes a drug’s mechanism of action and its therapeutic effects. Pharmacodynamics also gives us an indication of how the drug concentration or dosage relates to the subsequent extent of its therapeutic effects.1,2,4

Pharmacokinetics describes the absorption, distribution, metabolism, or biotransformation and elimination (through excretion) of drugs, in other words, the effects of body processes on drug molecules, as a function of time (i.e. as measured over time). Some authors refer to the four highlighted processes as the ADME processes, however, some substitute elimination with excretion.1,5

Pharmacology therefore answers the following questions:

- What type of drug are we dealing with, what is the nature and composition of the drug, and what may be expected from the drug in question?
- What will happen to the drug once it enters the body?
- What will the effects of the drug (both wanted and unwanted) be on the body?
- How will the drug interact with foodstuffs, other drugs and substances?
- What is the therapeutic significance of the drug in question?

How do drugs work?

This is a very complex question and it has no simple answer. Firstly, as described in the previous section, we need to have a thorough understanding of the term “drug”, and secondly, attempt to relate this definition to the way in which drugs produce their effects in the broadest sense of the concept.

To begin with, drugs need to influence body functions to have a therapeutic effect.

Pharmacology is very closely related to physiology, since drugs influence physiological processes in the body in one way or another. However, drugs cannot create new cell or tissue functions. Qualitative influencing of body physiology is not possible, but drugs have the ability to influence body physiology in a quantitative way by positively influencing whatever the disease process has altered in a
negative way. Drugs may increase or decrease body functions, depending on their mechanisms of action. In other words, they may increase or stimulate physiological processes, or decrease, inhibit or block such processes.\textsuperscript{1,3}

For drugs to exert their effects on body physiology, they need to interact with specific target areas, generally referred to as drug receptors (i.e. the targets of drug action). The interaction between drugs and their receptors is chemical in nature, making organic chemistry and biochemistry important foundation sciences in drug studies.\textsuperscript{1,3}

These drug receptors, or drug targets, are three-dimensional molecular complexes, capable of interacting with drug molecules to form chemical bonds between them. Compared to the complex structure of proteins and protein-containing biological macromolecules, such as glycoproteins and lipoproteins in the body, drugs are relatively simple and small micromolecules. It is the complex structure of these protein-containing macromolecules (large molecules) that makes them ideal drug targets.

There are different types of drug target or drug receptor types:\textsuperscript{1,3}

Specific ligand receptors

Drugs that bind to these receptors target the binding sites of the normal, physiological, signal-transmitting substances that directly influence cell and tissue functioning. These receptors are found throughout the body and occur in all glandular tissue (endocrine and exocrine), muscle tissue (cardiac, skeletal and smooth muscle) and nervous tissue. Protein-containing macromolecules provide these receptor sites. The signal-transmitting substances are also referred to as ligands.

These ligands may be:
- Neurotransmitters (e.g. dopamine, noradrenaline and acetylcholine);
- Hormones (e.g. adrenaline, oxytocin and insulin); or
- Autacoids (e.g. histamine, serotonin and the prostaglandins).\textsuperscript{1,3}

Most of our therapeutically useful drugs exert their effects on body physiology by influencing specific sets of ligand receptors. Receptors of a similar type may be grouped together to form receptor systems that reflect their ligand-binding capabilities (e.g. the adrenergic and cholinergic receptor systems).\textsuperscript{1}

These receptors may be broadly defined as being cellular molecules that interact with ligands and drugs to establish chemical bonds with them. Once bonded, the ligand-receptor complex (or drug-receptor complex) that has now formed, brings about biochemical changes in the target cells and tissues, which then produce the desired biological effects.\textsuperscript{1,3}

Ligand receptors may be classified as being either membrane receptors or intracellular receptors:

Membrane receptors

These receptors are ligand-binding molecular structures that are found on the outer surface of the cell’s plasma membrane. In addition, they have effector sites on the internal surface of the membrane as well, and are therefore also referred to as transmembrane receptors.\textsuperscript{1,3}

Intracellular receptors

Intracellular receptors act as primary target areas for steroids (e.g. steroid hormones, such as androgens, oestrogens and corticosteroids) and the metabolites of vitamin D. These receptors may be cytoplasmic or nuclear (i.e. situated inside the nucleus of the cell) receptors.\textsuperscript{1,3}

Enzyme receptors

Some drugs interact with enzyme receptors as their targets and consequently inhibit the normal physiological functions of the enzymes in question. These drugs act as either competitive inhibitors by competing with the actual enzyme substrates, or as non-competitive inhibitors by changing the conformation of these enzymes.\textsuperscript{1,3}

Transport carrier receptors

Transport proteins (carriers) are involved in the facilitated diffusion and active transport of ions and neurotransmitters across plasma membranes. Drugs that bind to these carrier proteins will inhibit the proteins’ normal functioning by competing with the endogenous substrates that are supposed to be transported by the carriers in question.\textsuperscript{1,3}

Some drugs may bind to plasma and tissue proteins, making them pharmacologically inactive in their bonded state. From a pharmacological viewpoint these proteins do not constitute actual drug targets, but rather influence the distribution of the drugs in question.\textsuperscript{1,3}

More about this in Part 2…

Conclusion

Pharmacology is the scientific study of medicinal drugs and comprises two major subdivisions, namely pharmacodynamics and pharmacokinetics. With the exception of the novel biopharmaceutical agents, the majority of drugs are small-molecule, chemical compounds that have been pharmaceutically prepared and made into suitable dosage forms for human and animal consumption. Most drugs exert their pharmacological actions through drug-receptor interaction.

The next three articles in this series will focus on the principles of pharmacodynamics, and the basics of receptor pharmacology, as well as the pharmacokinetic processes of absorption, distribution, metabolism and excretion.
Pharmacology provides us with answers to the former question, while pharmacokinetics answers the latter one.

### Identify the four fundamental pharmacokinetic processes.

These are the so-called ADME-processes:
- A: Absorption
- D: Distribution
- M: Metabolism (or biotransformation)
- E: Excretion (some authors refer to “E” as Elimination).

### Describe the difference between a small-molecule, chemical agent and a biotechnology drug.

Drugs are chemical substances that influence physiological, including biochemical, or mental processes in the body. When used with discretion and vigilance, drugs will display their beneficial biological effects in the presence of physical or mental illness. Some drugs may even be used to prevent or diagnose disease.

Biopharmaceutical agents constitute a group of therapeutic agents that do not fit the traditional definition of drugs. In contrast to the chemical substances mentioned above, which are also referred to as small-molecule drugs or “traditional” pharmaceuticals, the biopharmaceutical agents are much bigger macromolecules produced through biotechnology, as opposed to simple extraction or chemical sourcing and manufacturing.

### Classify the major types of drug receptors.

Specific ligand receptors.
- Membrane receptors.
- Intracellular receptors.
- Enzyme receptors.
- Transport carrier receptors.

### Answers

**Give a brief definition of pharmacology and medicinal drugs.**

Pharmacology is the scientific study of drugs, where they come from, their nature, their chemical composition, their expected actions, their wanted and unwanted effects and their uses.

Drugs are the active ingredients of medicines. Therefore, drugs are pharmacologically active substances and are used in the manufacture of medication for human or animal consumption. Drugs may be used to prevent, diagnose and treat physical or mental illness, or alleviate some of the symptoms associated with such afflictions.

**Briefly explain the difference between the two major subdivisions of pharmacology.**

The two major subdivisions of pharmacology answer the two most fundamental questions that may be posed wherever drug therapy is concerned.

These questions are:

- What will the drug do to the body?
- What will the body do to the drug?