Drug administration & drug action and its complexity

Definition:

A very broad definition of a drug would include "all chemicals other than food that affect living processes." If the affect helps the body, the drug is a medicine. However, if a drug causes a harmful effect on the body, the drug is a poison. The same chemical can be a medicine and a poison depending on conditions of use and the person using it. Another definition would be "medicinal agents used for diagnosis, prevention, treatment of symptoms, and cure of diseases." Contraceptives would be outside of this definition unless pregnancy was considered a disease.

Disease Classification: A disease is a condition of impaired health resulting from a disturbance in the structure or function of the body. Diseases may be classified into the following major categories:

1) **Infections** caused by viruses, ricketsia, bacteria, fungi, protozoa and worms

2) **Allergic diseases** caused by antigens and foreign substances

3) **Metabolic disorders** caused by defects in the body's ability to carry out normal reactions - these may be hereditary, deficiency, and congenital defects

4) **Cance**r

5) **Toxic diseases** caused by poisons

6) **Psychosomatic and mental diseases**Chemotherapy, broadly defined, means the treatment of any disease by chemicals including infectious and non-infectious diseases. The original definition applied only to drugs which were used in the treatment of infectious diseases. The proper term for the treatment of non-infectious diseases is pharmacodynamics.

Mode of Drug Action

It is important to distinguish between actions of drugs and their effects. Actions of drugs are the biochemical physiological mechanisms by which the chemical produces a response in living organisms. The effect is the observable consequence of a drug action. For example, the action of penicillin is to interfere with cell wall synthesis in bacteria and the effect is the death of the bacteria. One major problem of pharmacology is that no drug produces a single effect. The primary effect is the desired therapeutic effect. Secondary effects are all other effects beside the

desired effect which may be either beneficial or harmful. **Drugs are chosen to exploit differences between normal metabolic processes and any abnormalities which may be present.** Since the differences may not be very great, drugs may be nonspecific in action and alter normal functions as well as the undesirable ones. This leads to undesirable side effects. The biological effects observed after a drug has been administered are the result of an interaction between that chemical and some part of the organism. Mechanisms of drug action can be viewed from different perspectives, namely, the site of action and the general nature of the drug-cell interaction.

l. Killing Foreign Organisms:

Chemotherapeutic agents act by killing or weakening foreign organisms such as bacteria, worms, viruses. The main principle of action is selective toxicity, i.e. the drug must be more toxic to the parasite than to the host.

2. Stimulation and Depression:

Drugs act by stimulating or depressing normal physiological functions. Stimulation increases the rate of activity while depression reduces the rate of activity. infectious diseases and cancer. (Sulfa drugs, Antibiotics) b) Pharmacodynamic agents - used in non-infectious diseases (Cholinergic, Adrenergic, Hallucinogenic, Sedatives) c) Miscellaneous agents (Narcotic Analgesics, Local Anesthetics)

Drug Names:

Drugs have three or more names including a: chemical name, brand or trade name, and generic or common name. The chemical name is assigned according to rules of nomenclature of chemical compounds. The brand name is always capitalized and is selected by the manufacturer. The generic name refers to a common established name irrespective of its manufacturer. In most cases, a drug bearing a generic name is equivalent to the same drug with a brand name. However, this equivalency is not always true. Although drugs are chemically equivalent, different manufacturing processes may cause differences in pharmacological action. Several differences may be crystal size or form, isomers, crystal hydration, purity-(type and number of impurities), vehicles, binders, coatings, dissolution rate, and storage stability.

Sites of Drug Action:

l. Enzyme Inhibition:

Drugs act within the cell by modifying normal biochemical reactions. Enzyme inhibition may be reversible or non reversible; competitive or non-competitive. Antimetabolites may be used which mimic natural metabolites. Gene functions may be suppressed.

2. Drug-Receptor Interaction:

Drugs act on the cell membrane by physical and/or chemical interactions. This is usually through specific drug receptor sites known to be located on the membrane. A receptor is the specific chemical constituents of the cell with which a drug interacts to produce its pharmacological effects. Some receptor sites have been identified with specific parts of proteins and nucleic acids. In most cases, the chemical nature of the receptor site remains obscure.

3. Non-specific Interactions:

Drugs act exclusively by physical means outside of cells. These sites include external surfaces of skin and gastrointestinal tract. Drugs also act outside of cell membranes by chemical interactions. Neutralization of stomach acid by antacids is a good example.

Drug Receptor Interactions

Introduction: The vast majority of drugs show a remarkably high correlation of structure and specificity to produce pharmacological effects. Experimental evidence indicates that drugs interact with receptor sites localized in macromolecules which have protein-like properties and specific three dimensional shapes. A minimum three point attachment of a drug to a receptor site is required. In most cases a rather specific chemical structure is required for the receptor site and a complementary drug structure. Slight changes in the molecular structure of the drug may drastically change specificity. Several chemical forces may result in a temporary binding of the drug to the receptor. Essentially any bond could be involved with the drug-receptor interaction. Covalent bonds would be very tight and practically irreversible. Since by definition the drug-receptor interaction is reversible, covalent bond formation is rather rare except in a rather toxic situation. Since many drugs contain acid or amine functional groups which are ionized at physiological pH, ionic bonds are formed by the attraction of opposite charges in the receptor site. Polar-polar interactions as in hydrogen bonding are a further extension of the attraction of opposite charges. The drug-receptor reaction is essentially an exchange of the hydrogen bond between a drug molecule, surrounding water, and the receptor site. Finally hydrophobic bonds are formed between non-polar hydrocarbon groups on the drug and those in the receptor site. These bonds are not very specific but the interactions do occur to exclude water molecules. Repulsive forces which decrease the stability of the drug-receptor interaction include repulsion of like charges and steric hindrance. Steric hindrance refers to certain 3-dimensional features where repulsion occurs between electron clouds, inflexible chemical bonds, or bulky alkyl groups. A **neurotransmitter** has a specific shape to fit into a receptor site and cause a pharmacological response such as a nerve impulse being sent. The neurotransmitter is similar to

a substrate in an enzyme interaction. After attachment to a receptor site, a drug may either initiate a response or prevent a response from occurring. A drug must be a close "mimic" of the neurotransmitter. An **agonist** is a drug, which produces a stimulation type response. The agonist is a very close mimic and "fits" with the receptor site and is thus able to initiate a response.

An **antagonist** drug interacts with the receptor site and blocks or depresses the normal response for that receptor because it only partially fits the receptor site and can not produce an effect. However, it does block the site preventing any other agonist or the normal neurotransmitter from interacting with the receptor site. A **neurotransmitter** has a specific shape to fit into a receptor site and cause a pharmacological response such as a nerve impulse being sent. The neurotransmitter is similar to a substrate in an enzyme interaction. After attachment to a receptor site, a drug may either initiate a response or prevent a response from occurring. A drug must be a close "mimic" of the neurotransmitter. An **agonist** is a drug which produces a stimulation type response. The agonist is a very close mimic and "fits" with the receptor site and is thus able to initiate a response. An **antagonist** drug interacts with the receptor site and blocks or depresses the normal response for that receptor because it only partially fits the receptor site and can not produce an effect. However, it does block the site preventing any other agonist or the normal neurotransmitter from interacting with the receptor site.

Central Nervous System

Introduction - Drugs Acting Upon the Central NervousSystem:

The central nervous system directs the functions of all tissues of the body. The peripheral nervous system receives thousands of sensory inputs and transmits them to the brain via the spinal cord. The brain processes this incoming information and discards 99% as unimportant. After sensory information has been evaluated, selected areas of the central nervous system initiate nerve impulses to organs or tissue to make an appropriate response. Chemical influences are capable of producing a myriad of effects on the activity and function of the central nervous system. Since our knowledge of different regions of brain function and the neurotransmitters in the brain is limited, the explanations for the mechanisms of drug action may be vague. The known neurotransmitters are: acetylcholine which is involved with memory and learning; norepinephrine which is involved with mania-depression and emotions; and serotonin.

Protein –Protein interactions

Protein–protein interactions (PPIs) refer to lasting and specific physical contacts established between two or more proteins as a result of biochemical events and/or electrostatic forces.

Commonly they are understood as physical contacts with molecular docking between proteins that occur in a cell or in a living organism in specific biomolecular contexts. Proteins rarely act alone. Many molecular processes within a cell are carried out by molecular machines that are built from a large number of protein components organized by their PPIs. These interactions are important for the interactomics system of the living cell and aberrant PPIs are the bases of multiple diseases, such as Creutzfeld-Jacob, Alzheimer's disease, and cancer.PPIs have been studied from different perspectives: biochemistry, quantum chemistry, molecular dynamics, signal transduction, among others. All this information enables the creation of large protein interaction networks – similar to metabolic or genetic/epigenetic networks – that empower the current knowledge on biochemical cascades and disease pathogenesis, as well as provide putative new therapeutic targets.

To describe the types of protein–protein interactions (PPIs) it is important to consider that proteins can interact in a "transient" way (to produce some specific effect in a short time) or to interact with other proteins in a "stable" way to build multiprotein complexes that are molecular machines within the living systems. A protein complex assembly can result in the formation of homo-oligomeric or hetero-oligomeric complexes. In addition to the conventional complexes, as enzyme-inhibitor and antibody-antigen, interactions can also be established between domain-domain and domain-peptide. Another important distinction to identify protein-protein interactions is the way they have been determined, since there are techniques that measure direct physical interactions between protein pairs, named “binary” methods, while there are other techniques that measure physical interactions among groups of proteins, without pairwise determination of protein partners, named “co-complex” methods.

Homo-oligomers vs. hetero-oligomers

Homo-oligomers are macromolecular complexes constituted by only one type of protein subunit. Protein subunits assembly is guided by the establishment of non-covalent interactions in the quaternary structure of the protein. Disruption of homo-oligomers in order to return to the initial individual monomers often requires denaturation of the complex. Several enzymes, carrier proteins, scaffolding proteins, and transcriptional regulatory factors carry out their functions as homo-oligomers. Distinct protein subunits interact in hetero-oligomers, which are essential to control several cellular functions. The importance of the communication between heterologous

proteins is even more evident during cell signaling events and such interactions are only possible due to structural domains within the proteins.

Stable interactions vs. transient interactions

Stable interactions involve proteins that interact for a long time, taking part of permanent complexes as subunits, in order to carry out structural or functional roles. These are usually the case of homo-oligomers (e.g. cytochrome C), and some hetero-oligomeric proteins, as the subunits of ATPase. On the other hand, a protein may interact briefly and in a reversible manner with other proteins in only certain cellular contexts – cell type, cell cycle stage, external factors, presence of other binding proteins, etc. – as it happens with most of the proteins involved in biochemical cascades. These are called transient interactions. For example, some G protein-coupled receptors only transiently bind to Gi/o proteins when they are activated by extracellular ligands, while some Gq-coupled receptors, such as muscarinic receptor M3, pre-couple with Gq proteins prior to the receptor-ligand binding.

Covalent vs. non-covalent

Covalent interactions are those with the strongest association and are formed by disulphide bonds or electron sharing. Although being rare, these interactions are determinant in some posttranslational modifications, as ubiquitination and SUMOylation. Non-covalent bonds are usually established during transient interactions by the combination of weaker bonds, such as hydrogen bonds, ionic interactions, Van der Waals forces, or hydrophobic bonds.

Factors that regulate protein–protein interactions

- Protein concentration, which in turn are affected by expression levels and degradation rates;
- Protein affinity for proteins or other binding ligands;
- Ligands concentrations (substrates, ions, etc.);
- Presence of other proteins, nucleic acids, and ions;
- Electric fields around proteins.
- Occurrence of covalent modifications.

Carbohydrate–protein interactions

Carbohydrate–protein interactions form the basis of specific recognition of carbohydrates by lectins. Carbohydrates are important biopolymers and have a variety of functions. Often carbohydrates serve a function as a recognition element. That is, they are specifically recognized by other biomolecules. Proteins which bind carbohydrate structures are known as lectins. Compared to the study of protein–protein and protein–DNA interaction, it is the recent even those scientists get to know the protein–carbohydrate binding.

Many of these interactions involved carbohydrates found at the cell surface, as part of a membrane glycoprotein or glycolipid. These interactions can play a role in cellular adhesion and other cellular recognition events.

Classification

Generally, there are two types of protein carbohydrate binding important in biological processes: Lectin and antibody.

Lectin

Lectin is a kind of protein that can bind to carbohydrate with their carbohydrate recognition domains (CRDs). We could use different CRD to classify them.

C-**type**

Ca2+ is required to activate the binding. Ca2+ binds to the protein and carbohydrate by non covalent bond. Mannose-binding protein (MBP) contains the C-type CRD.

P-**type**

Two types mannose-6-phosphate can recognize phosphorylated saccharide. One is cation-dependent and the other does not require cation to activate.

I-**type**

I-type lectin named from the immunoglobulin-like domain. Sialoadhesin is one of the I-type lectin, which binds specifically to sialic acid.

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