Prodrugs:

Definition, Advantages, and Classification

Prodrugs:

A Prodrug can be defined as "pharmacologically inert chemical derivative that can be converted *in vivo*, enzymatically and/or a chemical transformation, to the active drug that exerts the intended therapeutic effect(s)". Ideally, the prodrug should be converted to the parent drug as soon as it reach its goal, and then followed by the subsequent rapid metabolism and/or elimination of the released active group.

Prodrug design can be highly effective for solving many pharmaceutical and pharmacokinetic barriers in clinical drug application such as stability, solubility, permeability and targeting problems in drug discovery and development.

Prodrug advantages:

Prodrugs are used as a way to:

- Increase lipid or water solubility
- Improve that taste of a drug to make it more patient compatible
- Alleviate pain when the drug is administered parenterally by injection
- Reduce toxicity
- Increase chemical stability
- Increase biological stability
- Change the length of the time of duration of action
- Deliver the drug to a specific site in the body

Prodrug classification:

There are potentially many methods of classifying prodrugs and these are based on the following aspects:

1. Therapeutic categories; for example, anticancer prodrugs, antiviral prodrugs, antibacterial prodrugs, non-steroidal anti-inflammatory prodrugs, cardiovascular prodrugs, etc.

2. Functional categories: this aspect used strategic approaches to circumvent deficiencies inherent to the active drug; for example, prodrugs for improving site specificity, prodrugs to bypass high first-pass metabolism, prodrugs for improving stability, prodrugs for reducing adverse effects, prodrugs for improving drug targeting, and prodrugs for improving absorption and bioavailability, or according to.

3. The nature of the chemical linkages, moieties or carriers, that are attached to the active drug to produce for example, ester, glucosidic, amide, carbonyl, and azo prodrugs, together with those used in what is known as the antibody-, gene-, virus-directed enzyme prodrugs therapies.

Depending upon the constitution, lipophilicity, method of bioactivation and the catalyst involved in the bioactivation process, prodrugs are classified into two categories, which are as follows:

- Bioprecursor or metabolic precursor's prodrugs: that contain no promoiety but is rather reliant on the metabolism by processes such as oxidation, reduction, phosphorylation, and sulfation activations to introduce the functionality necessary to create the desired active agent unlike the hydrolytic activation of the carrier-linked prodrugs.

➢ Carrier-linked prodrug: where the active agent have been attached through the metabolically labile linkage to another molecule (promoiety) which is not necessary for the activity, but may impart some desirable properties of the drug. Carrier-linked prodrug is the most important and widely used one.
Carrier-linked prodrug can be further subdivided into:

- Bipartate: composed of one carrier (group) attached to the parent drug.
- Tripartat: where the carrier group is attached via spacer linked to the parent drug.

While, the classification of the prodrug can also be done, depending upon the nature of carrier used, the carrier-linked prodrug may further be classified into:

➢ Double prodrugs, pro-prodrugs or cascade-latentiated prodrugs, where a prodrug is further derivatized in a fashion such that only enzymatic conversion to prodrug is possible before the latter can cleave to release the active drug.

➢ Macromolecular prodrugs, where macromolecules like polysaccharides, dextrans, cyclodextrins, proteins, peptides, and polymers are used as carriers. The development of macromolecular prodrugs of NSAIDs is advantageous because of the fact that these formulations show sustained release of drug, colon-targeted drug delivery, reduction in the administration frequency and better patient compliance.

➢ Site-specific prodrugs where a carrier acts as a transporter of the active drug to a specific targeted site.

➢ Mutual prodrug, where the carrier used is another biologically active drug instead of inert molecule. A mutual prodrug consists of two pharmacologically active agents coupled together so that each acts as a promoiety for the other agent and vice versa. The carrier selected may have the same biological action

as that of the parent drug and thus might give synergistic action, or the carrier may have some additional biological action that is lacking in the parent drug, thus ensuring some additional benefit. The carrier may also be a drug that might help to target the parent drug to a specific site or organ or cells or may improve site specificity of a drug. The carrier drug may be useful to overcome some side effects of the parent drug as well.

DRUG TARGETS

A **biological target** is anything within a living organism to which some other entity, like an endogenous ligand or a drug is directed and/or binds. Examples of common classes of biological targets are proteins and nucleic acids. The definition is context-dependent and can refer to the biological target of a pharmacologically active drug compound, the receptor target of a hormone (like insulin), or some other target of an external stimulus. The implication is that a target is "hit" by a signal and its behavior or function is then changed. Biological targets are most commonly proteins such as enzymes, ion channels, and receptors.

Mechanism

The external stimulus (*i.e.*, chemical substance) physically binds to the biological target.[1][2] The interaction between the substance and the target may be:

- noncovalent – A relatively weak interaction between the stimulus and the target where no chemical bond is formed between the two interacting partners and hence the interaction is completely reversible.
- reversible covalent - A chemical reaction occurs between the stimulus and target in which the stimulus becomes chemically bonded to the target, but the reverse reaction also readily occurs in which the bond can be broken.
- irreversible covalent - The stimulus is permanently bound to the target through irreversible chemical bond formation.

Depending on the nature of the stimulus, the following can occur:

- There is no direct change in the biological target, except that the binding of the substance prevents other endogenous substances such as activating hormone to bind to the target. Depending on the nature of the target, this effect is referred as receptor antagonism, enzyme inhibition, or ion channel blockade.
- A conformational change in the target is induced by the stimulus which results in a change in target function. This change in function can mimic the effect of the endogenous substance in which case the effect is referred to as receptor agonism (or channel or enzyme activation) or be the opposite of the endogenous substance which in the case of receptors is referred to as inverse agonism.

Drug targets

The term biological target is frequently used in pharmaceutical research to describe the native protein in the body whose activity is modified by a drug resulting in a specific effect, which may be a desirable therapeutic effect or an unwanted adverse effect. In this context, the

biological target is often referred to as a **drug target**. The most common drug targets of currently marketed drugs include:

- proteins
  - G protein-coupled receptors (target of 50% of drugs)
  - enzymes (especially protein kinases, proteases, esterases, and phosphatases)
  - ion channels
    - ligand-gated ion channels
    - voltage-gated ion channels
  - nuclear hormone receptors
  - structural proteins such as tubulin
  - membrane transport proteins
- nucleic acids

Drug target identification

Identifying the biological origin of a disease, and the potential targets for intervention, is the first step in the discovery of a medicine. This has been a great challenge for both academia and industry. Number of different approaches and technologies are reviewed.[8]

Databases

Databases containing biological targets information:

- Therapeutic Targets Database (TTD)
- DrugBank
- Binding DB

RECEPTOR- DRUG TARGET

Salbutamol- drug

Salbutamol is a highly selective β2-adrenergic receptor stimulating drug that has a bronchodilator effect. It is used to relieve bronchospasm in bronchial asthama, chronic bronchitis, emphysema and other airway resistance diseases.

General pharmacology:

► The chemical name of salbutamol is 1-(4-hydroxy-3-hydroxymethylphenyl)-2-(t-butylamino)-ethanol sulphate, molecular formula is $(C_{13}H_{21}NO_3)_2 \bullet H_2SO_4$ and molecular weight is 576.7.

► After oral administration, approximately 50% of salbutamol is absorbed from the intestinal tract with a slower onset of action, reaching a peak at about 2 hours after intake. After inhalation, salbutamol reaches the lungs directly and acts within 3-5 minutes with a peak at 15-20 minutes. Overall duration of action of salbutamol is 4-6 hours. It is metabolized in the intestinal tract and in the liver and is excreted via the urine.

Mechanism of action:

► Salbutamol stimulates β_2 adrenergic receptors which are predominant receptors in bronchial smooth muscle of the lung. Stimulation of β_2 receptors leads to the activation of enzyme adenyl cyclase that form cyclic AMP (adenosine-mono-phosphate) from ATP (adenosine-tri-phosphate). This high level of cyclic AMP relaxes bronchial smooth muscle and decreases airway resistance by lowering intracellular ionic calcium concentrations. Salbutamol relaxes the smooth muscles of airways, from trachea to terminal bronchioles.

► High level of cyclic AMP are also inhibits the release of bronchoconstrictor mediators such as histamine, leukotreine from the mast cells in the airway.

Usage:

1. Bronchospasm with reversible obstructive airway diseases

Salbutamol is indicated for the preventation or treatment of bronchospasm with reversible obstructive airway diseases such as

► Bronchial asthama

► Chronic obstructive pulmonary disease (COPD) which includes chronic bronchitis and emphysema

2. Exercise-induced bronchospasm

► Salbutamol is used for the prevention of exercise-induced bronchospasm.

3. Any other situations known to induce bronchospasm.