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Commentary

Role of Allosteric Modulators in Modern Drug Discovery

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INTERPRETATION

Most drugs today are designed to bind directly to the major active sites (also known as orthosteric sites) of biological targets. The drug binds to the active site of the biomolecule such as an Enzymes or receptors that cause inhibition or modification of the function of biomolecules. The binding of the drug to the active site of the enzyme prevents the binding of the substrate to that site and thus inhibits the function of the enzyme. Similarly, binding of an agonist or antagonist to the orthosteric site of a receptor can cause activation or inactivation of receptor function. Therefore, most drugs are designed to adapt to the major active sites of the biological target to elicit a therapeutic effect. This classic approach to drug design has been well studied and its effectiveness has been proven by the numerous successful drugs on the market. Many drugs have high affinity and high specificity for osteosteric binding sites, targeting specific diseases and disorders with high specificity. However, many enzymes or receptors with related functions can have very similar active sites, so adverse side effects can still occur. Another drawback of these drugs may be that they are complete inhibitors or activators instead of regulating the function of biomolecules.

The new approach to drug design is based on the effects of secondary binding sites. In this approach, small molecule drugs are designed to bind to the secondary binding site of the target biomolecule rather than the main orthosteric site. These secondary sites are called allosteric sites and the approach is called allosterism. Drugs that have the potential to succeed (called allosteric modulator) can bind to allosteric sites and remotely altering (or modifying) the conformation of the primary orthosteric binding site of the biological target. This conformational change can affect the binding of natural ligands to the orthosteric site of an enzyme or receptor protein in two ways:

Allosteric modification results in an enhancement in the binding affinity of the ligand with the orthosteric site and may result in an increase in signal or activity. The compounds that show such effects are referred to as Positive Allosteric Modulators (PAMs).

Allosteric modification can slow or block the binding of ligands to orthosteric binding sites, weakening signal or decreased activity. The compounds that cause such an effect are called Negative Allosteric Modulators (NAMs).

It is important to note that many compounds can bind to the allosteric site without affecting the binding properties of the orthosteric site. Therefore, not all allosteric binding sites are suitable targets for inducing favorable conformational changes. The design of an effective allosteric modulator depends on the identification of allosteric sites and the subsequent design of molecules that can bind to these sites and cause the desired conformational changes to the biomolecule of interest.

The drug discovery approach is much newer and still emerging, but allosteric modulators such as Cinacalcet (Amgen) for the treatment of hyperparathyroidism and Maraviroc (Pfizer) for the treatment of AIDS have already been approved. It has been developed and there are many candidates at different stages of development. Proponents of this approach point to many possibilities and benefits that can be achieved by adopting allosteric modulation to drug design. Some of the potential advantages are as follows:

- Unique allosteric sites can be identified to be narrower and more specific in targeting the disease through new drugs that may produce drugs with fewer side effects.
- There are many diseases in which drug therapy is lacking due to difficulty in designing drugs that interact with orthosteric sites or due to lack of specificity. The use of allosteric modulators may provide better alternatives for discovering new drugs to treat these disorders.
- Allosteric modulators may provide the ability to regulate drug effects to act like a dimmer, rather than acting as an on/off switch by being a complete inhibitor or activator.

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