Research and Reviews: Drug Delivery

Advances in Pharmacology of Purine and Pyrimidine Receptors

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Short Communication

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DESCRIPTION

Drug design for cell surface receptors has largely focused on either competitive agonist or antagonist ligands that occupy the principal (orthosteric) binding sites of these receptors, that is, the sites at which the native ligands for these receptors act. Recently, interest has grown in the modulation of clinically validated receptors by small molecules that act at allosteric sites, that is, those sites for binding on the receptor protein that are not identical with the orthosteric binding sites of the native ligands. Changeux and colleagues first introduced the concept of allosteric modulation of receptor action for the nicotinic cholinergic receptors, that is, channels for cations that are activated by the neurotransmitter acetylcholine. Now, the approach of allosteric modulation of the action of a native agonist has grown in importance for the ligand design and pharmacology of both G Protein-Coupled Receptors (GPCRs) and ligand-gated ion channels (LGICs). For example, two such agents that are already in clinical use for GPCR modulation are Cinacalcet and Maraviroc, which act as an allosteric agonist of the calcium sensing receptor and inhibitor of chemokine coreceptors required for HIV entry, respectively. The widely used benzodiazepines allosterically enhance the activation of GABAA chloride channels.

In the area of GPCRs, in particular, many therapeutic agents currently in use act as orthosteric agonists and antagonists, but there is a need to expand the ways in which GPCRs and other cell surface receptors may be modulated. Two major types of allosteric modulators for GPCRs have been defined: Positive Allosteric Modulators (PAMs), which increase the affinity, potency and/or efficacy of the agonist, and Negative Allosteric Modulators

(NAMs), which may decrease the above parameters. Further divisions based on pharmacological parameters are also relevant. For example, a PAM may only modulate the action of the native agonists, that is, magnify or enhance the effect of an endogenous molecular signal. Alternatively, it might have its own agonist action by binding to a site different from the binding site of the native agonist and would therefore be classified as an allosteric agonist [1,2].

There are several points of justification for studying allosteric modulation of cell surface receptors. First of all, the receptors are often widely distributed throughout the body-leading to problems of side effects when an orthosteric agonist is administered therapeutically. The action of a PAM would be expected to be more tissue- and event specific than the action of a stable, exogenously administered orthosteric agonist, which would circulate throughout the body. Second, allosteric modulators may have an inherently greater chance of achieving subtype selectivity than the orthosteric ligands. In the case of some GPCRs, such as muscarinic acetylcholine receptors, the design of subtype-selective orthosteric agonists and antagonists has progressed very slowly until recently, largely because the amino acid residues within the orthosteric binding site are highly conserved if not identical across the subtypes. It is thought that greater subtype selectivity could be obtained by targeting other regions of the receptors, such as the Extracellular Loops (ELs) in Class A GPCRs where there is more structural variation than in Transmembrane Domains (TMs). In fact, this approach has resulted in muscarinic receptor modulators of great selectivity. Another possible advantage of PAMs over orthosteric agonists is the possibility to alter the spectrum of second messenger effects or produce a bias toward a particular pathway based on conformational variation of the receptor in its activated state. Finally, an additional potential advantage of allosteric modulators is the preferential activation of receptors in areas of low receptor density or low receptor reserve. A full agonist or a partial agonist will always activate areas where receptor density is highest. In contrast, it may be possible to have preferential action on areas of lower receptor density with PAMs, as was illustrated for the A1 Adenosine Receptor (AR) [3-5].

Assay methods used to identify allosteric modulators of the ARs have included both radioligand binding and functional assays. Initially, screening typically has consisted of detecting an increase in the level of binding of radioligand to membranes expressing a given receptor subtype. Functional assays using an EC50 or EC80 concentration of an orthosteric ligand are used to screen for modulators, particularly in industry.

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