7. Allosterism, Orthosteric Site, Allosteric Site, Allosteric Modulator, and Bitopic Ligand

François Noël, July 2016

The term **"allosteric"** was first introduced by Jacques Monod and François Jacob in 1962 to describe the phenomenon of interaction between two topographically distinct sites within the same enzyme, mediated through the transmission of a conformational change. In 1980, De Lean, Stadel, and Lefkowitz applied this concept of allosteric interaction to explain signal transduction in metabotropic receptors, within the so-called ternary complex model (agonist-receptor-G protein).

Currently, allosterism has become a focus of many pharmacological studies, both in academia and in pharmaceutical companies, because of its great potential for developing more selective and/or safer drugs. Indeed, there is a greater likelihood of obtaining selective compounds by targeting allosteric sites than orthosteric sites, whose structures are generally highly conserved among different subtypes of the same receptor, as well illustrated in the case of muscarinic receptors. It is noteworthy that maraviroc was the first allosteric drug approved for clinical use, acting as a neutral allosteric modulator ("antagonist") of the CCR5 chemokine receptor.

On the other hand, a safer profile may result from the fact that an allosteric modulator tends to produce a more physiological effect, by preserving the temporal and spatial pattern associated with neurotransmitter release, and an effect that is limited to a certain level, regardless of dose escalation (the ceiling effect).

In light of the above, it seemed timely to recall some definitions related to this important topic, which prompted a nomenclature recommendation by the IUPHAR (Christopoulos et al., 2014). Another motivation for this choice is the important role played by Arthur Christopoulos in that IUPHAR article and in research on new allosteric drugs, as he will be one of the three keynote speakers at our upcoming SBFTE congress celebrating the 50th anniversary of our Society.

DEFINITIONS

Orthosteric site: the binding site on the receptor that is recognized by the endogenous agonist of that receptor.

Allosteric site: a binding site on the receptor that does not overlap with, is spatially distinct from, but is conformationally linked to the orthosteric site.

Allosteric modulator: a ligand that modifies the action of an orthosteric agonist, an endogenous activator, or an antagonist by binding to an allosteric site on the receptor. A **positive allosteric modulator** increases the action (affinity and/or efficacy) of an orthosteric agonist, activator, or antagonist, whereas a **negative allosteric modulator** decreases the action (affinity and/or efficacy) of an orthosteric agonist, activator, or antagonist.

Bitopic ligand: a hybrid molecule that simultaneously occupies both an orthosteric site and an allosteric site on a receptor via two pharmacophoric moieties (one acting as an orthosteric ligand and the other as an allosteric ligand).

References

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