The secret lives of GPCRs

As described in a recent review by Graham Milligan [1], new technologies such as 'high-content assays' have enabled us to see previously unknown, or at least not easily quantified, G-protein-coupled receptor (GPCR) behaviours. Historically, drug efficacy was defined in terms of tissue response, because this was the only means available to detect ligand-induced changes in receptors. However, new assay techniques have shown that, in addition to activating G-proteins, GPCRs display a range of behaviours, including homodimerization, heterodimerization, internalization and interaction with a host of cytosolic and membrane proteins. Many of these behaviours are associated with an agonistic response but not necessarily with G-protein activation [2]. In fact, dissociations have been observed – for example, the cholecystokinin (CCK) receptor antagonist D-Tyr-Gly-[(Nle^{28,31},D-Trp^{30})cholecystokinin-26-32]-phenethyl ester does not produce receptor activation but does produce a profound receptor internalization [3].

There are at least two reasons why expanded detection systems for ligand-induced changes in receptor behaviour are potentially beneficial for drug discovery. The first is that, thermodynamically, there is reason to believe that ligand binding to receptors also biases the conformations of the receptor (i.e. affinity and efficacy are correlated) [4]. For instance, the new technique, fluorescence lifetime spectroscopy, shows Gaussian distributions for the halftime of a covalently bound fluorescent probe on the β_2-adrenoceptor [5], indicating an ever-changing protein environment (an ensemble of tertiary conformations). The presence of the neutral antagonist, alprenolol, changes the distribution of lifetimes (β_2-adrenoceptor conformations) indicating that, although no effect of this ligand is seen with conventional functional assays, protein conformation is still changed by the binding of the ligand. In other words, if a given assay does not detect altered receptor efficacy, this does not necessarily mean that no change has occurred. A dramatic example of this is the prevalence of inverse agonism, a phenomenon thought to be rare when first discovered by Costa and Hertz [6], and now becoming extremely common with the increasing availability of the assay required to view the effect (constitutively active receptor systems).

The second reason why expanded detection might be of benefit is that some of the non-G-protein-associated activities of GPCRs could be therapeutically useful. For example, internalization of the chemokine receptor, CCR5, is theoretically an excellent strategy for the prevention of HIV-1 infection [7]. By screening with the expanded eyes of high-content assays, ligand effects on the secret lives of GPCRs will hopefully lead to new generations of therapeutically useful drugs.

References

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