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Introduction

G-protein-coupled receptors in drug discovery

How many times have you heard it said that the GPCR superfamily is *the* most fruitful area for drug discovery by attracting over 30%, 40%, or an even higher percentage of the revenue for today's prescription drugs? Not so. In fact, the market share for GPCR-related drugs has been falling since those heady days of the 1970s and 1980s when selective agonists and antagonists for GPCRs activated by the biogenic amines (noradrenaline, dopamine, histamine, and 5-hydroxytryptamine) were discovered. The early successes in the monoamine field have not been matched, as yet, by successes for those receptors where the endogenous ligand is significantly more complex, such as for peptide-activated receptors. This is particularly disappointing because many of the recently deorphanised receptors fall into this class.

In a global pharmaceutical market hovering around the $500 billion mark, sales of GPCR ligands are estimated to be $50 billion, equating to only 10% of current sales. Of the 35 GPCR prescription drugs in the top 200 best sellers and accounting for around $40 billion in sales (2003), 24 operate at monoaminergic receptors, 8 are angiotensin-II receptor blockers, 2 are peptide analogues acting at somatostatin and FSH receptors, with a leukotriene antagonist completing the list. Starkly, leaving aside the AT_1 receptor, there is not a single blockbuster small molecule (sales >$500 million) operating at peptide-activated GPCRs. Huge opportunities await those groups able to design selective small molecules and thence restore GPCR drugs to their previous eminence. One such opportunity that turned out to be only modestly successful was the approval two years ago of an NK_1 antagonist but only for chemotherapy-induced emesis and not for the more lucrative antidepression market.

So what has gone wrong? Certainly for the class B GPCRs, for which peptides are the exclusive ligands, and for many class A receptors, there is increasing evidence that receptor binding and activation represent two distinct steps, each associated with its own interaction domain. For example, for the CRF receptor, kinetic data have been interpreted in terms of a two-site model where the NT and extracellular loops provide the initial "collision complex" with the C-terminal region of the peptide ligand, CRF. This complex undergoes an intramolecular reorganization which finally places the N-terminus of CRF in juxtaposition with the helical bundle of the receptor. Only when this second state is achieved does binding lead to receptor activation and downstream signal transduction. In turn, this might suggest two separate opportunities for small-molecule binding, although medicinal chemists would prefer the comfort of interacting with the helical domain since that has provided a well-defined binding site so successful in the design of drugs for the biogenic amine receptors. The conceptual problem in achieving this objective is that the small molecule now has to compete with what is essentially an intramolecular peptide ligand which is all set to activate the receptor as soon as the small-molecule antagonist is discharged in accordance with its dissociation rate from the receptor. The alternative is less attractive because it relegates the discovery problem to interference of a protein–protein interaction which may not be so readily amenable to a small-molecule approach.

The end result is that drug-like, small-molecule ligands for the new wave of GPCRs of therapeutic interest are only now beginning to emerge. The following papers describe some new developments in both receptor structure and ligand design.

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