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CHEMOGENOMICS

A change of tactic

Somatostatin (SST) is a peptide hormone involved in the regulation of the endocrine system, neurotransmission and cell proliferation. SST signals through five well-characterized and distinct G-protein-coupled receptors (GPCRs). Given that each receptor has different properties, the lack of selectivity of current SST-receptor modulators (and their short half-life) has limited the ability to exploit the therapeutic potential of this receptor family.

Now, using an elegant chemogenomics approach, Rainer E. Martin and colleagues have designed the first, selective non-peptidic small-molecule antagonist of the SST-receptor subtype 5 (sst_5); a receptor that is known to activate NMDA (*N*-methyl-D-aspartate) receptor function as well as regulate hormone secretion. The rationale demonstrated in their approach might also be used generally in the development of more drug-like, selective GPCR modulators.

Rather than using established approaches for identifying SST receptor ligands, based on knowledge of a tetrapeptide motif that is required for SST to exert its biological activity, or large-scale high-throughput screening (HTS), the authors used a different tactic. By carrying out a focused screen of drugs that target GPCRs in which amino acids of the drug-binding site share notable homology to the ligand-binding site of the sst_5 receptor, they identified three biogenic amine receptor ligands that exhibited micromolar affinity against the sst_5 receptor. One of them, astemizole — a second-generation antihistamine — was selected as a seed structure to develop a more potent and selective sst_5 receptor antagonist.

Structure–activity relationship studies guided the optimization of the compound. Specific chemical modifications not only conferred a nanomolar binding affinity for the sst_5 receptor and improved its antagonistic activity, but also eliminated its original activity towards the histamine 1 receptor. Furthermore, astemizole's hERG (also known as KCNH2) liability, which is associated with a risk of serious cardiovascular side effects, was significantly reduced. The selectivity, potency and metabolic stability of the resulting compound highlights the ability of this approach to provide an efficient alternative to conventional HTS for the identification of new GPCR ligands.

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ORIGINAL RESEARCH PAPER Martin, R. E. *et al.* Discovery of the first nonpeptidic, small-molecule, highly selective somatostatin receptor subtype 5 antagonists: a chemogenomics approach. *J. Med. Chem.* **50**, 6291–6294 (2007).
FURTHER READING Guba, W. *et al.* From astemizole to a novel hit series of small-molecule somatostatin 5 receptor antagonists via GPCR affinity profiling. *J. Med. Chem.* **50**, 6295–6298 (2007).