TARGET VALIDATION

Target for the modern-day ills?

The role of melanin-concentrating hormone (MCH) — a cyclic 19-amino-acid neuropeptide — in feeding behaviour has been well established in recent years, leading to interest in the possibility of antagonizing its action as a therapeutic approach to obesity. Now, as Borowsky *et al.* report in *Nature Medicine*, antagonists of MCHR1 — one of the two G-protein-coupled receptors (GPCRs) that mediate the effects of MCH — might have promise not only in the management of obesity, but also as a treatment for depression and anxiety.

Screening of a GPCR-biased compound collection led to the identification of SNAP-7941, a nanomolar inhibitor of MCHR1 that has 1,000-fold selectivity over the other receptor for MCH, and also over other GPCRs associated with food intake, such as the receptor for neuropeptide Y. Systemic pre-treatment with SNAP-7941 inhibited the increase in food intake elicited by MCH, supporting a role for MCHR1 in mediating MCH-stimulated food intake.

But would pharmacological blockade of MCHR1 reduce basal body weight, or would compensatory mechanisms come into play? The authors found that acute treatment with SNAP-7941 decreased palatable food intake in rats, and that chronic treatment resulted in a marked, sustained decrease in body weight in rats with diet-induced obesity, providing strong support that MCHR1 is a viable target for the treatment of obesity.

Although MCH has been studied most extensively in relation to food intake and body weight, the distribution of SNAP-7941-binding sites (assessed using [^{3}H]-labelled SNAP-7941) and MCHR1 immunoreactivity (determined previously) in regions of the brain such as the amygdala, nucleus accumbens, dorsal raphe and locus coeruleus, indicated that MCH might be involved in mood regulation and anxiety. To investigate this, Borowsky *et al.* evaluated SNAP-7941 in three animal models of depression and/or anxiety, and compared the results with those for clinically approved drugs. In the rat forced-swim test, which is indicative of antidepressant activity, the profile of SNAP-7941 was similar to the selective serotonin-reuptake inhibitor fluoxetine, and in the rat social-interaction test, which is a model of anxiety, the profile of SNAP-7941 was indicative of an anxiolytic activity analogous to the prototypical benzodiazepine chlordiazepoxide. Finally, in the guinea-pig maternal-separation vocalization test, which is predictive of anxiolytic and antidepressant activity, the responses to SNAP-7941 were comparable to those of buspirone. So, although the role of MCH in human psychiatric disorders remains largely unknown, it seems that further assessment of MCHR1 antagonists for the treatment of depression and/or anxiety could be warranted.

Peter Kirkpatrick

References and links

ORIGINAL RESEARCH PAPER Borowsky, B. *et al*. Antidepressant, anxiolytic and anorectic effects of a melanin-concentrating hormone-1 receptor antagonist. *Nature Med.* **8**, 825–830 (2002)

IN BRIEF

OBESITY

Activation of central melanocortin pathways by fenfluramine.

Heisler, L. K. *et al. Science* **297**, 609–611 (2002)

D-Fenfluramine (D-FEN) was once widely prescribed as an appetite suppressant, but was withdrawn owing to cardiac complications in a subset of patients. Heisler *et al.* show that D-FEN-induced anorexia requires activation of melanocortin pathways in the central nervous system, which have a well-established role in food intake. Their results provide a mechanistic explanation for the anorexic activity of D-FEN, and indicate that drugs that target these melanocortin pathways might prove to be effective anti-obesity treatments with fewer side effects.

COMPUTATIONAL CHEMISTRY

Identification of potent and novel α4β1-antagonists using *in silico* screening.

Singh, J. S. *et al. J. Med. Chem.* **45**, 2988–2993 (2002)

The integrin α4β1 has a key role in the inflammatory response, and has been implicated in the pathology of diseases such as asthma, multiple sclerosis and rheumatoid arthritis. A potent and selective inhibitor for α4β1 based on a peptide sequence from the natural ligand for α4β1 had previously been identified, but its peptidic nature resulted in rapid clearance in animals. Singh *et al.* used a three-dimensional pharmacophore model of the peptidic inhibitor to search a chemical database for structures that satisfy the constraints of the model, and identified a potent non-peptidic inhibitor of α4β1, which showed encouraging activity in a sheep model of asthma.

HIGH-THROUGHPUT SCREENING

Screening inhibitors of anthrax lethal factor.

Tonello, F. *et al. Nature* **418**, 386 (2002)

New and specific therapies to combat the potential threat of anthrax are urgently needed. Tonello *et al.* describe an assay for detecting inhibitors of lethal factor, a proteolytic enzyme that is one of the three components of anthrax toxin. The substrates for lethal factor that the authors created allow detection of proteolytic activity using visible-light or fluorescence detectors in a high-throughput format.

LEAD IDENTIFICATION

SAR by MS: a ligand based technique for drug lead discovery against structured RNA targets.

Swayze, E. E. *et al. J. Med. Chem.* 2002 Jul 27 (doi: 10.1021/jm0255466)

RNAs are attractive drug targets, but high-throughput screening against RNA targets has yielded active compounds at much lower rates than those usually observed for protein targets. Swayze *et al.* used mass spectrometry to determine structure–activity relationships for weak-binding 'motif' compounds, which were used to guide the linkage of these motifs into high-affinity ligands for a subdomain of bacterial 23S ribosomal RNA.