PSYCHIATRIC DISORDERS

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 an experimental model of depression, 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 a model of anxiety and depression, the responses to SNAP-7941 were comparable to those to 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, Associate Editor,
Nature Reviews Drug Discovery

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.* 15 July 2002 (doi:10.1038/nm741)

PRION DISEASES

Behavioural clues to TSEs

One of the problems in diagnosing transmissible spongiform encephalopathies (TSEs) is that the clinical symptoms often do not manifest themselves until quite late in the progression of the disease. However, as Dell'Omo *et al.* report in the *European Journal of Neuroscience*, mice that are infected with different prion strains show significant changes in circadian activity long before any clinical signs appear; moreover, the nature of these changes seems to depend on the prion strain.

The authors infected mice with scrapie prion strain 139A or ME7, or the bovine spongiform encephalopathy (BSE) strain 301C. Using an automated tracking system, the mice were monitored continually from seven weeks after infection. The most pronounced difference between strains was seen during the night, when mice are most active. Mice that were infected with strain 301C or ME7 showed a persistent depression of nocturnal activity, right from the beginning of the monitoring period. Strain-139A-infected mice, on the other hand, initially showed similar levels of activity to controls, but became hyperactive towards the time of onset of clinical symptoms. Also, from week 11 onwards, the 301C-infected mice were significantly less active than those infected with ME7.

The authors believe that their monitoring protocol could be scaled up for use in larger animals, such as sheep, and this might have important implications for agriculture. For example, in the United Kingdom, there is some concern that BSE has spread into sheep. Unfortunately, the symptoms of BSE are difficult to distinguish from those of scrapie, which has been present in sheep for many years and is not known to pose a significant threat to human health. If different prion strains are found to cause distinct early changes in circadian activity in sheep, behavioural monitoring could provide a useful diagnostic tool to distinguish between BSE and scrapie.

Heather Wood

References and links

ORIGINAL RESEARCH PAPER Dell'Omo, G. *et al.* Automated home cage monitoring of mice infected with BSE and scrapie differentiates early behavioural changes according to prion strain. *Eur. J. Neurosci.* 2002 (doi:10.1046/j.1460-9568.2002.02128.x)

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WEB SITES

Encyclopedia of Life Sciences: http://www.els.net/prion diseases

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