IN BRIEF

MOOD DISORDERS

Anxiolytic- and antidepressant-like profiles of the galanin-3 receptor (Gal3) antagonists SNAP 37889 and SNAP 398299.

Swanson, C. J. *et al. Proc. Acad. Natl Sci. USA* **102**, 17489–17494 (2005)

Stathmin, a gene enriched in the amygdala, controls both learned and innate fear.

Shumyatsky, G. P. *et al. Cell* **123**, 697–709 (2005)

Novel targets for mood disorders have been revealed by two recent papers. In the first, the authors show that galanin, a peptide known to be implicated in anxiety and depression, mediates its effects through the galanin-3 receptor. The authors found that acute administration of two small-molecule Gal3-antagonists to mice improved their social interaction and reduced anxiolytic and depressive behaviours, and worked synergistically with, and in a similar manner to, 5-hydroxytryptamine (5-HT) antagonists. The second paper identified a gene that encodes stathmin, a microtubule-formation inhibitor expressed at high levels in the amygdala and in structures that convey information about learned and innate fear. Stathmin-null mice were less able to learn new fear than wild-type mice and failed to recognize danger. In addition to stathmin's potential as an anti-anxiolytic drug target, ablation of its activity in mice generates a model that could be useful in the development of anti-anxiolytic agents.

AUTOIMMUNE DISEASE

Inhibition of FLT3 signaling targets DCs to ameliorate autoimmune disease.

Whartenby, K. A. *et al. Proc. Acad. Natl Sci. USA* **102**, 16741–16746 (2005)

Most approaches to treating autoimmune diseases focus on the direct suppression of unregulated autoreactive T cells. The authors of this paper took a different approach by selectively targeting dendritic cells, which are precursors of T cells that differentiate in response to FLT3 ligand. Inhibition of FLT3 signalling using small-molecule tyrosine kinase inhibitors induced apoptosis in mouse and human dendritic cells, and improved established disease in a model of multiple sclerosis.

NEUROLOGICAL DISEASES

DISC1 and PDE4B are interacting genetic factors in schizophrenia that regulate cAMP signaling.

Millar, J. K. *et al. Science* **310**, 1187–1191 (2005)

The *disrupted in schizophrenia 1* (*DISC1*) gene has been implicated in schizophrenia and other affective disorders but its role in disease progression is unknown. The authors of this paper have shown that a translocation in the gene encoding phosphodiesterase-4B (PDE4B) also seems to be a candidate susceptibility factor for schizophrenia, and propose that this results from the role of PDEs in the regulation of cAMP, which is involved in learning, memory and mood. Further investigation revealed that DISC1 interacts with a domain of PDE4B and that increasing levels of cAMP causes a dissociation of this complex and resultant increase in PDE4B activity. The authors speculate that genetic variations in these two genes will result in altered cAMP catabolism that manifests as psychiatric disorders.

OBESITY

An appetizing target

The discovery of hormones regulating appetite — specifically the appetite-suppressant leptin and the appetite-stimulant ghrelin — generated optimism that drugs for the treatment of obesity would soon follow. But extensive research on the roles of these peptide hormones in the pathways that control body weight has not led to an effective drug therapy. The identification of a new appetite-suppressing hormone, obestatin, and its receptor described by Zhang and colleagues provides new insights into how appetite-regulation hormones elicit their effects that could be key in the development of a treatment for obesity.

Ghrelin, which is produced in the gut by the posttranslational modification of a prohormone, was thought to be the last of the key genes involved in the regulation of body weight. However, while searching databases of known peptide hormones for potential hormone derivatives, Zhang and co-workers concluded that processing of proghrelin produces a second peptide hormone. They subsequently isolated this ghrelin-associated hormone from rat stomach and named it obestatin. To investigate the effect of obestatin on food intake, a synthetic obestatin peptide was injected into rat brain and gut. After treatment with obestatin, rats consumed ~50% less food. Obestatin also suppressed weight gain and slowed the passage of digested food from the stomach.

Zhang and colleagues then went on to identify the cognate receptor of obestatin. Ghrelin binds to growth hormone secretagogue receptor (GHSR), a G-protein-coupled receptor (GPCR), and the authors therefore proposed that the target of obestatin would be an orphan GPCR. Indeed, using I^{125}-radiolabelled obestatin the authors identified the target of obestatin to be GPR39.

The isolation of obestatin also sheds light on the mechanisms that underlie hormonal regulation of body weight. Deletion of the gene encoding ghrelin would be expected to suppress appetite; however, knockout of this gene has almost no effect on growth and appetite. It is now clear that knockout of the gene encoding ghrelin also deletes obestatin, which suggests an intricate balance in the activities of these two hormones in weight regulation.

The prevalence of obesity is on the increase worldwide. Understanding how obestatin and ghrelin interact to regulate weight could lead not only to an effective treatment for obesity, but also for other eating disorders such as anorexia nervosa.

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ORIGINAL RESEARCH PAPER Zhang, J. V. *et al.* Obestatin, a peptide encoded by the ghrelin gene, opposes ghrelin's effects on food intake. *Science* **310**, 996–999 (2005)
FURTHER READING Crowley, V. E. F., Yeo, G. S. H. & O'Rahilly, S. Obesity therapy: altering the energy intake-and-expenditure balance sheet. *Nature Rev. Drug Discov.* **1**, 276–286 (2002)