Disease Models & Mechanisms

RESEARCH HIGHLIGHTS

Introducing fat fish for anti-obesity drug screening

Rodent models of obesity can be used to address the systemic and multi-organ effects of excessive fat storage, but smaller animals are more suitable for large-scale genetic screening. However, measuring crucial metabolic parameters such as blood glucose, triglycerides and cholesterol has been difficult in commonly used non-mammalian models such as worms and flies. Chu et al. now report a transgenic zebrafish model of obesity overexpressing a constitutively active form of human AKT1. AKT is a kinase that functions in multiple cellular processes, including adipogenesis, and is central to the insulin signalling pathway. The zebrafish that was developed expresses AKT1 under the control of a skin-specific promoter, but the transgene is also expressed in several pre-adipocyte cell types, possibly owing to integration-positional effects. Compared with control fish, adult AKT1-transgenic zebrafish were larger and had enhanced adipogenesis, increased lipid content, and upregulated expression of adipokines and inflammatory markers. Moreover, they had elevated blood triglycerides and glucose intolerance, which are early indicators of metabolic syndrome. These results introduce AKT1-transgenic zebrafish as a powerful model for high-throughput screening for anti-obesity drugs.

The serotonergic feeding-regulatory circuit: learning from worms

Serotonin has emerged as a key neurotransmitter that regulates feeding behaviour. Targeting the serotonergic circuitry has therapeutic potential for human obesity, but the key molecules that regulate this circuitry are largely unknown. In Caenorhabditis elegans, it has been shown that serotonin enhances feeding behaviour, and that genetic ablation of tryptophan hydroxylase (tph-1; expressed in certain types of neuron and required for serotonin synthesis) reduces feeding. Cunningham et al. dissected this feeding circuit in more detail to identify additional, evolutionarily conserved components that control feeding behaviour. They showed that deletion of tph-1 in chemosensory ADF neurons, but not in NSM pharyngeal neurons, reduces feeding behaviour. The circuit was found to require SER-5, a serotonin receptor, and hlh34, the worm homologue of human SIM1, which encodes a transcription factor expressed in the human paraventricular nucleus (a brain region crucial for maintaining energy homeostasis). Serotonin produced by ADF neurons was found to increase feeding behaviour by inhibiting the activity of AMP-activated kinase (AMPK), another conserved regulator of energy balance, in hlh34-expressing neurons. AMPK inhibition led to increased glutamate neurotransmitter release by hlh34-expressing neurons, stimulating regulation by glutamate-responsive pharyngeal neurons. Finally, the authors demonstrate using rat hippocampal neurons that at least some aspects of this feeding-regulatory circuit also operate in mammals.

Bariatric surgery for T2D in obesity

The increasing incidence of obesity brings a parallel increase in type 2 diabetes (T2D), a metabolic complication of excess body weight. Despite recent improvements in pharmacotherapy, T2D symptoms are not normalised in up to 50% of patients, meaning a continued high risk of additional serious complications. Bariatric surgery, which involves the removal or re-routing of parts of the stomach and/or intestine, is known to provide significant weight-loss in the morbidly obese. However, whether these procedures can improve uncontrolled T2D, particularly in moderately obese individuals, has been unclear. Now, Schauer et al. report the first controlled trial comparing the results of bariatric surgery with medication versus medication alone in obese subjects with uncontrolled T2D. After 12 months, patients that underwent bariatric surgery had lost more weight and had decreased their medication use, whereas those receiving medication alone had lost very little weight and had increased their medication use. Although glycaemic control improved in all groups, 42% of those in the surgery cohort had normalised blood glucose, compared with only 12% in the medication alone group. Although larger studies will be needed to assess long-term outcomes, this study suggests that bariatric surgery combined with medication is a promising therapy for obese individuals with T2D. S.A.

