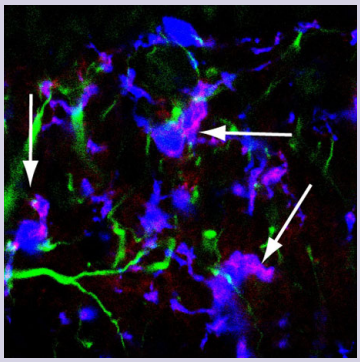


High-fat diet rapidly induces hypothalamic inflammation in mice

One of many theories explaining obesity proposes that weight gain is caused by dysfunction of the hypothalamic neurons that regulate energy homeostasis. A possible cause of neuronal dysfunction is inflammation. Obesity is associated with adipose-tissue inflammation; whether the brain is also affected has been unclear. Based on previous observations, Yi et al. examined the brains of mice that had been fed a high-fat diet (HFD) for ~16 weeks for signs of inflammation. In addition to activated migroglia (the immune cells of the brain), they found an accumulation of IgG specifically in the arcuate nucleus (ARC) of the hypothalamus. This was caused by diet and not obesity per se, because signs of hypothalamic inflammation were not observed in *ob/ob* mice on a standard diet. The effects of diet on the ARC were rapid, and began to appear as early as 2 weeks after exposure to a HFD. These results provide support that hypothalamic neuropathy promotes diet-induced obesity and suggest that targeting inflammation in the brain might be a promising avenue for therapy. **Page 686**

Glucocorticoids and T2D: insight from a new rat model

Increased levels of glucocorticoids (GCs), which are endogenous stress-induced steroid hormones such as corticosterone, are associated with type 2 diabetes (T2D), but whether they contribute to the development of the condition has been unclear. Shpilberg et al. addressed this issue by developing a Sprague-Dawley rat model to study the combined effect of GCs and a high-fat diet (HFD). They found that rats on a HFD and treated with a GC succumbed to rapid-onset diabetes, whereas glycaemia was near normal in rats on a HFD or with GC treatment alone. Combined treatment also led to increased food intake, extensive central adiposity and fatty liver. These data suggest that increased levels of GCs promote the development of T2D and other obesity-associated complications. Thus, exogenous GCs – which are used to treat a range of immunological conditions – should be used with caution. **Page 671**

High corticosterone levels contribute to T2D in the Goto-Kakizaki rat

Compared with humans, several inbred rodent strains have naturally high levels of circulating glucocorticoids (GCs), which can influence the development of type 2 diabetes (T2D). Thus, GC levels and their effects need to be accounted for in rodent studies of T2D. Beddow and Samuel assessed the involvement of corticosterone in T2D in the Goto-Kakizaki rat, a non-obese, spontaneously diabetic strain for which information on GCs was not previously available. They found that Goto-Kakizaki rats have higher levels of corticosterone than a control strain, and that drug-mediated lowering of corticosterone levels normalised plasma glucose and improved insulin sensitivity. Thus, future studies that use this established model of T2D – and others with naturally high circulating levels of GCs – should take the effects of GCs into account. **Page 681**

Altered inflammatory responses in mouse models of obesity

Obesity is associated with increased incidence and severity of various types of infection. In addition, it is well documented that obesity causes chronic, low-level inflammation, which is thought to contribute to many of obesity's complications. Studies of genetic obesity models have shed some light on how obesity influences inflammatory responses, but models of diet-induced obesity (DIO) have not been well characterised in this respect. Lawrence et al. compared responses to bacterial endotoxin, an acute inflammatory stimulus, in control mice, a model of genetic obesity (*ob/ob*) and a model of DIO. Both obesity models had impaired immune responses to the endotoxin, but there were notable differences that might help to better understand inflammatory responses in obese humans. **Page 649**

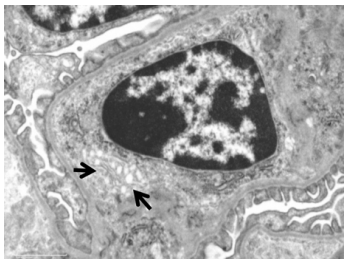
Prader-Willi syndrome: measuring cardiovascular risk factors

The association between obesity and cardiovascular disease is thought to be caused by obesity-induced inflammation, oxidative stress and alterations in plasma lipoproteins, such as the protective high-density lipoprotein (HDL). Ferretti et al. examined these parameters in healthy controls, obese individuals and obese subjects with Prader-Willi syndrome (PWS), the most common genetic form of obesity. They found that levels of lipid hydroperoxides were higher in both of the obese cohorts, and that the activity of paraoxonase-1 (PON1), an HDL-associated antioxidant enzyme, was decreased. A marker of inflammation and the physicochemical properties of HDL were also altered in the obese cohorts. These results indicate that obesity in humans – whether induced by diet or genetics – is associated with oxidative stress, altered properties of HDL and inflammation. They also suggest that HDL and PON1 are worth examining in the context of obesity-associated cardiovascular disease. **Page 698**

Obesity-associated kidney cancer: new clues from Wistar rats

The link between obesity and kidney cancer is well documented, but the underlying mechanisms are unclear. Stemmer et al. now uncover some important candidate factors in a study showing that the severity of renal pathology correlates with adiposity in Wistar rats. They compared three groups: lean rats on a standard diet, rats on a high-fat diet (HFD) that were susceptible to diet-induced obesity (DIO), and rats on a HFD that were partially resistant to DIO. Rats susceptible to DIO had the highest incidence of early-stage kidney cancer, and pro-tumorigenic pathways involving STAT3 and mTOR seemed to be involved in its development. Kidneys in DIO-susceptible mice also showed signs of inflammation, such as white-blood-cell infiltration and cytokine production. These data introduce a new model for studying the link between obesity and kidney cancer, and provide early data on potential therapeutic targets. **Page 627**

'POKO mice' enable studies of obesity-associated kidney disease



Obese individuals are at high risk of developing kidney disease, which can lead to renal failure requiring dialysis or transplant. Few models of obesity-associated kidney disease exist, so investigating the association has been a challenge. Martínez-García et al. now report a model that enables the study of kidney disease in the context of obesity. They crossed *ob/ob* mice (which store large amounts of fat) with mice lacking PPARγ (which are impaired in generating fat tissue) to generate 'POKO mice', which have high circulating levels of glucose and fat. At just 4 weeks old, POKO mice show kidney dysfunction associated with inflammation, fibrosis and lipid accumulation – all signs of advanced kidney disease. Kidney pathology advances to severe by 12 weeks. These data introduce the POKO mouse as a new model of obesity-associated kidney disease, and indicate that glucolipotoxicity can accelerate the condition. **Page 636**

A PPARα agonist improves metabolic parameters in obesity

Drug development for obesity has been fraught with failures and false-starts, in part owing to the complex pathways that govern energy homeostasis. One strategy is to intervene in key pathways using synthetic agents that mimic the action of endogenous molecules. Decara et al. now report that elaidyl-sulfamide, a molecule based on the anorectic lipid oleoylethanolamide (OEA), reduces food intake, body weight, plasma cholesterol and markers of hepatic dysfunction in obese rats. Similar to OEA, elaidyl-sulfamide was found to act as a PPARα agonist. However, in line with the ability of OEA to negatively regulate insulin signalling, chronic elaidyl-sulfamide treatment induced insulin resistance. This study suggests that chemical modelling of OEA is a promising avenue for drug development, providing that the effects of related compounds on insulin signalling can be overcome or are found to be negligible in humans. **Page 660**

Linking postnatal stress with metabolic disease in adulthood

Increasing evidence indicates that early-life stress contributes to metabolic disorders later in life. Paternain et al. studied this link in rats by exposing them to postnatal stress (periods of maternal separation) and then assessing their susceptibility to diet-induced metabolic dysfunction later in life. Their results show that maternal separation caused a differential response to a high-sucrose diet and altered the expression of several key metabolic genes in adult rats. Further studies could unravel the underlying mechanisms, with the aim of developing nutritional strategies that counteract the effects of early-life stress on metabolism in adults. **Page 691**

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