

Obesity— is it all in the mind?

The more developed world is in the middle of an obesity epidemic. Overconsumption of the wrong type of food and lack of exercise are often cited as the main causes, but neuroscientists are beginning to show that malfunctioning hypothalamic neurons can also lead to obesity.

One molecule that has generated a lot of interest is leptin, Barry Levin (Department of Veterans Affairs Medical Center, East Orange, NJ, USA) told delegates at the 32nd annual meeting of the Society of Neuroscience (Nov 6, 2002, Orlando, FL, USA). Levin's research team has found that some rats are more prone to obesity than others because of the way their brains respond to leptin.

Obesity-prone rats put on weight after only 1 week of being fed a high fat diet, but other rats are more resistant to gaining weight, even though plasma concentrations of leptin rise in both groups. Levin's group has shown that hypothalamic neurons in obesity-prone rats are less responsive to glucose and leptin, suggesting that these animals are predisposed to store calories when food is available (*Am J Physiol* 2002; **283**: R941–48). "The obesity-susceptible rats seem to undergo brain and nervous-system reorganisations that re-establish new body-weight set points", Levin says. "They defend their weight gain when their food intake is reduced, and when fed ad libitum again, regain their weight back up to the new level." This genetic predisposition makes it virtually impossible for obesity-prone rats to lose weight once they become obese. "It is likely", says Levin, "that brain development is also affected by both genetic and environmental factors before or shortly after birth so that maternal obesity can produce further obesity in genetically predisposed offspring."

Until recently, no one knew whether leptin acts directly within the hypothalamus to stimulate the gonadotropin-releasing hormone (GnRH)–luteinising hormone (LH) system. However, in recent experiments, Hajime Watanobe (International University of Health and Welfare,

Otawara, Tichigi, Japan) perfused the hypothalamus of fasting rats with leptin and showed that GnRH, LH, and α melanocyte-stimulating hormone (α -MSH) were released (*J Physiol* 2002; **545**: 255–68). "This is the first time that anyone has demonstrated that leptin can act on both the cell bodies and axon terminals of GnRH neurons to stimulate the release of the neurohormone in vivo, and they also suggest that α -MSH may play a significant intermediary role in linking leptin and GnRH secretion", Watanobe told *The Lancet Neurology*.

Another neuroendocrine product, neuropeptide Y (NPY), is creating interest as a regulator of appetite and food intake. In September, Margaret

Rights were not granted to include this image in electronic media. Please refer to the printed journal.

Dr Ray Clark and Mervyn Geff, SPL

Obesity research hots up

Morris and co-workers (University of Melbourne, Victoria, Australia) showed that hypothalamic neurons from diabetic rats released far less NPY in vitro in response to low glucose concentrations than did control animals. Next, the researchers induced hypoglycaemia in vivo with an insulin injection and showed that NPY concentrations in the paraventricular nucleus decreased in diabetic rats but increased in control animals (*Diabetologia* 2002; **45**: 1332–39). "We still have much to learn about the mechanisms and pathways involved, but this may help to explain why some human diabetics do not get the signal to eat when their blood sugar falls: diabetics may experience severe hypoglycaemic episodes because their hypothalamus does not release enough NPY during hypoglycemia", says Morris.

Stephen Bloom's research group (Imperial College, London, UK) has shown that peptide YY (PYY), an

agonist of the NPY2 receptor, is released from the gut after a meal in direct proportion to the calorie content of the meal; intraperitoneal injection of PYY in rats inhibits food intake and reduces weight. "This effect seems to be mediated through the arcuate nucleus: intra-arcuate injection of PYY inhibits food intake in rats, and also inhibits electrical activity of NPY nerve terminals, thus activating adjacent pro-opiomelanocortin neurons that release melanocortin, which decreases appetite", explains Bloom. Follow-up experiments have confirmed that PYY has similar effects in human beings: infusion of normal postprandial concentrations of PYY decreases appetite and reduces food intake by 33% after 24 h (*Nature* 2002; **418**: 650–54). According to Michael Schwartz (University of Washington, Seattle, WA, USA) the work of Bloom's group helps to clarify how the arcuate nucleus translates input from diverse hormonal signals into behavioural and metabolic responses that powerfully influence the energy-balance equation. "Changes in body weight are communicated to the brain by the hormones leptin and insulin, which inhibit the NPY expressing neurons", says Schwartz. Ghrelin, the hormone secreted by the stomach as soon as it is empty, can also stimulate food intake by activating these neurons. "The new insights are useful but many questions remain to be answered", warns Schwartz.

Although multiple classes of new antiobesity medications may soon be developed, it is unlikely that any one approach will prove to be a magic bullet. However, David Cummings (University of Washington, Seattle, WA, USA) predicts that "customised cocktails of several agents used in combination with interventions that reduce signalling by ghrelin or increase signalling at the neuronal melanocortin, leptin or insulin receptors may enable obesity to be managed much as we now manage other polygenic disorders such as hypertension".

Kathryn Senior