SYSTEMS NEUROSCIENCE

The stress of dieting

Many readers will have experienced that it is all too easy to regain the weight lost after a diet, and that experiencing stress somehow makes high-calorie foods particularly tempting. Bale and colleagues now provide a link between yo-yo dieting and stress by showing that in mice, food restriction alters stress and feeding pathways in the brain, and promotes binge eating of high-fat foods upon subsequent exposure to stress.

The authors used a mouse model of moderate caloric restriction that produces a 10–15% reduction in body weight. They found that 3 weeks of food restriction sensitized the hypothalamus–pituitary–adrenal stress axis: calorie-restricted mice had higher basal corticosterone levels and increased corticosterone release in response to restraint stress compared with control mice. Interestingly, expression of the gene encoding corticotrophin-releasing factor (*Crf*) in the bed nucleus of the stria terminalis (BNST) — a brain area where stress and reward pathways intersect — was decreased after caloric restriction and did not return to normal after chow re-feeding. In accordance with this finding, methylation of the *Crf* promotor was decreased in the BNST and remained so after re-feeding. In a different diet model, withdrawal from a high-fat diet had similar effects on *Crf* expression and methylation patterns.

The authors next examined whether these changes affected subsequent eating behaviour of previously restricted mice after they had been placed back on a normal diet. In non-stress conditions, both control and previously restricted mice displayed binge eating when exposed to high-fat food for 1 hour. However, when mice were exposed to chronic variable stress, previously restricted mice consumed more calories and ate more high-fat food than control mice, with intake increasing over the course of the 10-day experiment.

The authors reasoned that diet-induced activation of the stress system might have downstream effects on brain feeding pathways that could drive the increased consumption of high-fat food. They therefore measured levels of the orexigenic hormones melanin-concentrating hormone (MCH) and orexin in the lateral hypothalamus. Expression of both MCH and orexin was increased in previously restricted mice, but not in control mice, that had access to the high-fat diet. Treatment with an MCH receptor 1 antagonist decreased chow caloric intake in previously restricted mice but not in control animals, suggesting that this antagonist might have therapeutic potential in preventing weight gain after dieting.

These findings suggest that even moderate dieting induces a stress state and permanently alters *Crf* expression in the BNST. The precise role these changes have in subsequent stress-induced binge eating and MHC and orexin expression remain to be established — CRF reduction in the BNST might be a compensatory mechanism aimed at preventing further weight loss — but they suggest that avoiding stress after dieting might increase the chance of keeping off the weight.

Ezzie Hutchinson

ORIGINAL RESEARCH PAPER Pankevich, D. E. *et al.* Caloric restriction experience reprograms stress and orexigenic pathways and promotes binge eating. *J. Neurosci.* **30** 16399–16407 (2010)