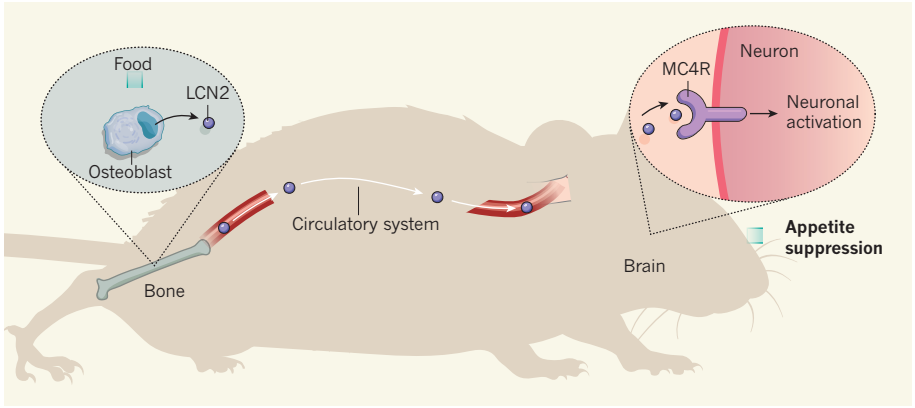

Figure 1 | A bone–brain axis modulates hunger. Mosialou *et al.*[1] report that, after mice eat a meal, absorbed nutrients are sensed by bone-forming cells called osteoblasts, which respond by releasing the glycoprotein lipocalin 2 (LCN2). LCN2 enters the bloodstream and circulates around the body, passing into the brain's hypothalamus. Here, the glycoprotein binds to melanocortin 4 receptor (MC4R) proteins on neurons. Neuronal activation by MC4R binding induces a signalling pathway that leads to loss of appetite.

after a meal. This treatment suppressed the appetites of wild-type mice, which lost weight compared with untreated control animals. Daily LCN2 injections in obese mice greatly reduced their weight gain and improved the ability of insulin to stimulate glucose uptake into cells.

Because feeding behaviour is controlled by the brain, the authors measured the amount of LCN2 in various brain regions, and found that it was most abundant in the brainstem and hypothalamus — regions that control feeding behaviour. When LCN2 was injected directly into the brain, it suppressed feeding as effectively as it did in the blood. The researchers concluded that LCN2 produced in bones circulates in the blood, crosses the blood–brain barrier and becomes selectively enriched in regions of the brain associated with appetite suppression (anorexia).

The discovery of a new hormone, especially one derived from bone, is itself intriguing, but Mosialou *et al.* set out to complete the story by identifying the receptor protein responsible for LCN2-induced anorexia. Clues to where this receptor might be found came from the authors' observation of LCN2 enrichment in the hypothalamus, combined with the fact that one of the best-established anorexia-promoting pathways is the signalling pathway involving α-melanin-stimulating hormone (α-MSH)[5]. In this pathway, α-MSH is produced by neurons in the hypothalamus and suppresses appetite by interacting with the melanocortin 4 receptor (MC4R), a member of a protein family called G-protein-coupled receptors.

Thus, the researchers explored the possibility that LCN2 somehow mimics α-MSH signalling. Indeed, they found that, *in vitro*, LCN2 stimulated production of an intracellular signalling molecule, cyclic AMP, by cells that expressed any one of three melanocortin receptors (MC1R, MC3R or MC4R), but not in cells lacking these receptors; this finding supports the idea that LCN2 binds to melanocortin receptors. Of these receptors, MC4R is expressed in the brainstem and hypothalamus and has been linked to feeding behaviour[5]. The affinity of LCN2 for MC4R binding was similar to that of α-MSH, and LCN2 could compete with α-MSH for binding to MC4R, despite the fact that the two molecules have no obvious similarities.

Further proof that LCN2 promotes anorexia by activating MC4R (Fig. 1) came from Mosialou and colleagues' demonstration that LCN2 bound to slices of hypothalamus in which MC4R is known to reside, but not to slices from mice lacking MC4R. Most importantly, they showed that LCN2 had no biological effects on food intake or glucose metabolism in mice lacking MC4R.

People with mutations in MC4R are often obese[6], and the authors showed that some of these people have elevated levels of LCN2 in their blood compared with weight-matched people without MC4R mutations. This result suggests that signalling from the brain to the bones controls LCN2 production in an attempt to establish homeostasis.

Although Mosialou *et al.* concentrated their efforts on the binding of LCN2 to MC4R in the hypothalamus, these receptors are also abundant on the vagus nerve, which projects from most internal organs to the hindbrain[7], where it can activate a neural circuit that promotes anorexia[8]. These vagal MC4Rs are more accessible to circulating hormones than are hypothalamic receptors, because they do not lie behind the blood–brain barrier. As such, they may be involved in the everyday appetite suppression induced by LCN2 after a meal.

It is well known[9] that sepsis, a condition caused by bacteria, or experimentally induced by injecting rodents with bacterial lipopolysaccharide molecules, produces profound anorexia. LCN2 is robustly induced in many cells by this condition; hence, it may also contribute to the anorexia caused by sepsis[2].

Overall, it is remarkable that hormones can

50 Years Ago

Several people have speculated on the thesis that if a sufficiently high concentration of an insect sex pheromone could be maintained in the atmosphere the sexes could not find each other for mating purposes … Their conclusion was that this could lead to control or possibly eradication of the species … We have for the first time obtained experimental confirmation that pre-mating communication between the sexes can be disrupted by permeating the atmosphere with an insect pheromone … The successful disruption of male orientation to females may be caused by sensory and (or) central nervous system adaptation to the pheromone … The result of this experiment indicates that economic control of an insect over large areas may be possible by behavioural control using sex pheromones.
From *Nature* 18 March 1967

100 Years Ago

Mr. Moullin divides tumours by their mode of origin into two classes: one due to the sudden awakening of the innate reproductive power of the tissues, in virtue of which they give birth to "buds" that grow into tumours; the other due to details of structure not being carried out so completely as they ought to be. The distinguishing feature of the former class of tumours is their independence: they grow quite irrespective of the tissue in which they develop … Development is the influence which restrains the potentiality possessed by the cells of the tissues to multiply indefinitely, and is due to chemical influences. All that is needed, then, for tumour formation is some exciting cause, mechanical or chemical, to give the growth a start.
From *Nature* 15 March 1917