antiosteogenic (it reduces bone mass). The finding led to speculation that increased bone mass in obese people might result not from an adaptive response to the stress of added pounds, but from resistance to leptin's antiosteogenic activity, just as resistance to leptin's appetite-reducing effects characterizes most obesity[4]. Writing in *Cell*, Takeda *et al.*[5] have delved deeper into the way in which leptin reduces bone mass under normal circumstances.

Leptin is released into the bloodstream in proportion to the amount of body fat. It regulates the body's energy balance — the difference between food intake and energy expenditure — by binding to certain receptor proteins, which are expressed on, and regulate the activity of, specific neurons in the hypothalamus of the brain (Fig. 1a). These molecular and neuronal targets of leptin were identified through a combination of genetic, pharmacological and neuroanatomical approaches. Takeda *et al.*[5] have now applied the same range of techniques to look at how leptin affects bone. Their first, remarkable conclusion is that, although leptin influences both energy balance and bone mass by acting on the hypothalamus, the two processes involve different proteins and neurons.

For example, many of leptin's effects on appetite and energy expenditure involve the activation of neurons found in one region of the hypothalamus, the arcuate nucleus. These neurons produce the protein pro-opiomelanocortin, the precursor of α-melanocyte-stimulating hormone. When this hormone is released from the neurons, it binds to the melanocortin-4 receptor on other neurons, thereby activating them and leading to effects on energy balance[6]. When these receptors are absent or blocked in mice, the animals become severely obese and no longer respond to the energy-regulating effects of leptin[7]. Yet, as Takeda *et al.* show, these mutants apparently still respond to leptin's bone-density-reducing effects, as their bone mass does not increase. Similarly, when the authors damaged these arcuate neurons by administering monosodium glutamate, leptin — injected into the brain — no longer affected energy balance, but still reduced bone density. This convincingly demonstrates that the weight- and bone-regulating neuronal pathways are different.

It is still not known which leptin-responsive neurons regulate bone, although one clue came from an earlier study of neuropeptide Y and the Y2 receptor protein[8]. Neuropeptide Y was known to be secreted by certain neurons in the arcuate nucleus (a process that is inhibited by various hormonal regulators, including leptin). It then binds to the Y1–Y5 receptors on other neurons, thereby regulating feeding and the activity of the involuntary nervous system. The study in question[8] found that Y2 receptors were also involved in regulating bone synthesis and mass, because mice lacking these hypothalamic receptors had increased bone mass. This suggested a role for involuntary output from the hypothalamus, mediated through nerves on which the Y2 receptor is expressed, in regulating bone.

In theory, this involuntary output could trigger the release of other hormones that reach bone through the blood circulation, or it could affect bone directly. Takeda *et al.* have tackled this question. First, they propose that no circulating hormone (besides leptin, that is) is involved. Next, they use various approaches to demonstrate a role for the sympathetic nervous system — a major arm of the involuntary nervous system — in controlling bone density. It was known that leptin activates sympathetic-nerve output in rodents[9], but it was not suspected that bone biology was also affected by this.

Takeda *et al.* now propose the following model (Fig. 1b). Leptin activates hypothalamic nerves (identity unknown), which in turn activate sympathetic nerves. These extend into the bone, where they stimulate release of the neurotransmitter noradrenaline, which then stimulates β2-adrenergic receptors on osteoblasts (bone-forming cells), inhibiting osteoblast activity.

The authors invoke several lines of evidence to support this model. First, dopamine-β-hydroxylase-deficient mice, which cannot synthesize noradrenaline[10], have high bone density, presumably because the bone-forming cells remain active. Although such mice respond to leptin by reducing their fat mass substantially, there is no effect on bone. Second, leptin-deficient mice show a reduced rate of firing of sympathetic nerves and high bone mass; drugs that stimulate β-adrenergic receptors do not affect the body fat of these mice, but do cause severe loss of bone — apparently by reducing the rate of bone formation by osteoblasts. Finally, and perhaps most surprisingly, when mice are given the β-adrenergic-receptor blocker propranolol, which is commonly used to treat cardiovascular ailments, bone mass is increased. This occurs even in mice with depleted oestrogen levels following removal of the ovaries, which otherwise causes bone mass to plummet.

How readily can we extrapolate these

Biomechanics

Frogs in and out of phase

K. D'AOÛT, ANTWERP

Many animals use several different gaits — patterns of locomotion that change abruptly at a critical speed. People walk to go slowly and run to go fast. Horses and other quadrupedal mammals walk, trot and gallop. In flight, birds and bats have slow and fast gaits. Many fish swim slowly with their fins and fast with their whole bodies. On land, frogs crawl slowly and hop faster.

Now we learn from Sandra Nauwelaerts and Peter Aerts that frogs also change gait when they swim (*J. Zool.* **258,** 183–188; 2002). Frogs swim by kicking water backwards with their webbed feet. Usually they kick with both hind legs simultaneously (in-phase swimming), but Nauwelaerts and Aerts find that in slow swimming the hind legs move alternately (out-of-phase swimming). The subject of their attention, the species *Rana esculenta*, is shown here in static pose.

Measurements of oxygen consumption show that humans and horses change gait at speeds at which the slower gait becomes less energy-efficient than the faster one. The same may be true for flying birds. Fish, however, seem to change gait because their fin muscles cannot provide enough power for high speeds. Do swimming frogs save energy by changing gait, or do they have to change gait to develop enough power to swim fast?

From measurements on video sequences, Nauwelaerts and Aerts calculate that out-of-phase swimming uses less power than in-phase swimming at the same speed. During in-phase swimming, the animal accelerates by kicking with both feet, then decelerates as it brings its feet forward for the next kick. During out-of-phase swimming, the frog's speed fluctuates much less because each leg is brought forward while the other is kicking. Hydrodynamic drag is approximately proportional to the square of the speed, so speed fluctuations increase the mean drag.

This argument suggests that out-of-phase swimming should be the more economical gait at all speeds. However, it may be less effective at generating thrust, because the feet interact when they are used together. So frogs may be obliged to use the less economical gait to generate enough thrust to swim fast. **R. McNeill Alexander**

R. McNeill Alexander is at the School of Biology, University of Leeds, Leeds LS2 9JT, UK.
e-mail: r.m.alexander@leeds.ac.uk