

# News & views

## Metabolism

# Exercise molecule burns away hunger

Tahnbee Kim & Scott M. Sternson

A metabolite called Lac-Phe is associated with exercise-induced ‘muscle burn’. This molecule has now been shown to reduce food intake after exercise in mice, racehorses and humans, and to trigger weight loss in obese mice. **See p.785**

Long bouts of exercise can promote weight loss – as long as increased energy expenditure is not compensated for by later food intake. On page 785, Li *et al.*<sup>1</sup> describe a product of metabolism (a metabolite molecule) that is released during exercise and subsequently suppresses appetite in mice. The authors’ findings open up a route for better understanding of the physiological consequences of exercise.

Li *et al.* used a strategy known as an unbiased metabolomic approach to identify molecules whose circulation in the blood increases after intense exercise in mice, racehorses and humans. The group discovered that one metabolite in particular, Lac-Phe, was greatly increased in each species, consistent with a previous report in humans<sup>2</sup>. Lac-Phe is a conjugate of lactate and phenylalanine. The former is a metabolic by-product of strenuous exercise, responsible for the burning sensation in over-exerted muscle, whereas the latter is an essential amino acid.

The group examined the metabolic and behavioural effects of Lac-Phe in mice given a high-fat diet. They injected these diet-induced

obese (DIO) mice with Lac-Phe at higher-than-physiological doses, which suppressed food intake for at least 12 hours. Li *et al.* showed that administration of Lac-Phe to DIO mice over 10 days resulted in reduced daily food consumption and body weight, which was specifically due to a decrease in fat tissue. By contrast, neither lactate or phenylalanine alone affected appetite, and Lac-Phe administration did not change the feeding behaviour of lean mice on a low-fat diet. These results demonstrate that increased circulating Lac-Phe suppresses feeding specifically in mice made obese by a high-fat diet.

Li *et al.* confirmed a previous finding<sup>2</sup> that Lac-Phe is produced by the enzyme carnosine dipeptidase 2 (CNDP2). They showed that Lac-Phe production by CNDP2 depends on the availability of lactate, which is consistent with the fact that the metabolite is generated by exercise. DIO mice that were genetically engineered to lack CNDP2 did not upregulate production of Lac-Phe in response to exercise. Notably, sedentary mutant animals exhibited no significant differences in food intake and

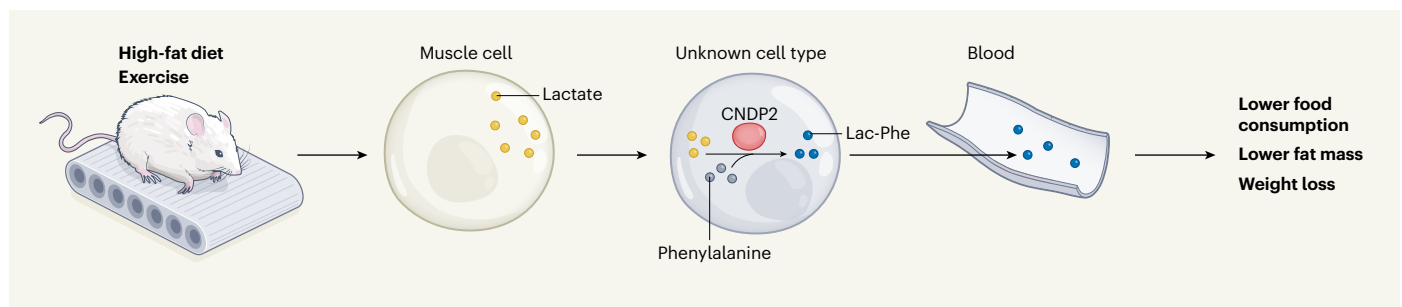
body weight compared with controls. This indicates that CNDP2 is not required for basal energy maintenance.

Finally, Li and colleagues examined how exercise affects body weight in mice fed a high-fat diet and simultaneously put on a daily exercise regime. Control animals maintained a stable weight under this regime. By contrast, mice lacking CNDP2 showed an increase in appetite and weight gain, because the animals ate more to compensate for their increased energy expenditure and because they were consuming an obesity-promoting diet. Thus, CNDP2-mediated production of Lac-Phe is an exercise-dependent process that promotes weight loss in mice fed high-fat food (Fig. 1).

These findings provide a connection between Lac-Phe production, appetite suppression and loss of body fat. However, the physiological pathway through which Lac-Phe acts remains to be uncovered. Li *et al.* reported that CNDP2 is expressed in several cell types in mice, with especially high levels in immune cells and epithelial cells, which line the body’s organs. Further research is required to determine whether these cell types or others are responsible for exercise-induced Lac-Phe biosynthesis.

That Lac-Phe suppressed food intake for 12 hours is interesting, given that the metabolite circulates in the blood for less than one hour after exercise. This suggests that Lac-Phe has long-lasting influences on signalling pathways that alter feeding behaviour. A Lac-Phe receptor protein and cell types in which that receptor is expressed remain to be identified.

Of particular interest is the potential interaction of Lac-Phe, directly or indirectly, with neurons that control eating behaviours. Neural circuits influence appetite through at least three distinct processes<sup>3</sup>: the energy-sensing system that maintains normal body function; satiety circuits that are highly sensitive to



**Figure 1 | A molecular pathway for Lac-Phe production.** Li *et al.*<sup>1</sup> studied male mice that undertook strenuous daily exercise and ate a high-fat diet. Exercise triggers production of the molecule lactate in muscle cells, and the authors showed that a metabolite molecule called Lac-Phe is produced from lactate and the amino acid phenylalanine by the enzyme CNDP2 in an unknown cell type – possibly, immune cells or epithelial cells. Lac-Phe passes into the blood, and is associated with reduced appetite, reduced fat mass and weight loss in these mice.

physiological stressors; and reward-driven appetite pathways. Modulation of any of these pathways could be consistent with the reported data. The fact that Lac-Phe reduces appetite selectively in mice fed a high-fat diet could reflect an influence on pleasure-driven eating, although this remains to be examined.

Lac-Phe is not the only appetite-suppressing molecule produced by exercise. Growth differentiation factor 15, peptide tyrosine-tyrosine and glucagon-like peptide-1 also inhibit food intake and are increased in humans after exertion<sup>4–6</sup>. These molecules also have other metabolic functions, influencing energy expenditure, insulin sensitivity and blood glucose levels. Chronic Lac-Phe administration improved the uptake of glucose from blood into tissues in DIO mice, although Li *et al.* posited that this was an indirect consequence of weight loss. Going forward, it will be interesting to assess whether Lac-Phe has a direct effect on glucose uptake by tissues – this would indicate roles for the metabolite beyond appetite suppression, such as potential involvement in nutrient use during exercise.

Some clinical studies have shown post-exercise appetite suppression in men, but there is less evidence to support this phenomenon in women<sup>6–9</sup>. Li *et al.* examined only male mice, so future studies should investigate Lac-Phe in females. More generally, it will also be important to examine the relationship between Lac-Phe levels in blood plasma during exercise and both appetite suppression and weight loss. Might Lac-Phe levels in plasma affect how well exercise can promote weight loss?

The evolutionary adaptive role of exercise-induced appetite suppression is intriguing. One possibility is that the type of strenuous exertion studied by Li and colleagues is indicative of a stressor that threatens immediate survival: energy intake is deprioritized because it is necessary only for longer-term survival. For example, it is better not to be distracted by hunger when trying to escape predators.

Li and colleagues' discovery marks a starting point from which to investigate molecular pathways for exercise-induced weight loss in overweight mice. In addition, the exercise-induced increase in plasma Lac-Phe levels in men points to possibilities for improving weight management in people, if the role of Lac-Phe signalling in appetite and body-weight regulation is shown to translate to humans. It should be noted, though, that many factors, such as social eating and easy access to high-calorie palatable food, can circumvent the effectiveness of any stand-alone intervention. Ultimately, multi-pronged strategies used together are likely to be the best way of combating obesity, regardless of whether the current findings are applicable to humans.

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### Nuclear physics

# Four neutrons might form a transient isolated entity

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An experiment firing helium-8 nuclei at a proton target has generated evidence that four neutrons can exist transiently without any other matter. But doubts remain, because the existence of such systems is at odds with theory. **See p.678**

To understand the nature of cohesion in any system, you have to push the system until it breaks. In the case of atomic nuclei, this means knowing when the short-range attractive nuclear force that acts between nucleons (protons and neutrons) surrenders to the repulsive long-range Coulomb force between protons, and the extent to which extreme proton-to-neutron ratios can exist in nature. Neutron stars are proof that huge gravitational forces can bind almost purely neutron matter, but whether the nuclear force can do so alone has been a long-standing question. On page 678, Duer *et al.*<sup>1</sup> 'break' a helium-8 nucleus in search of an answer to this question, and find evidence hinting at the existence of a transient system comprising only four neutrons.

The only bound system that contains two nucleons is the deuteron, a system with one proton and one neutron. This system is stabilized by the alignment of the intrinsic angular momenta of the proton and the neutron – something that is not possible for systems containing just two neutrons or two protons. Even more than not being bound, the two-neutron system also falls short of being a 'resonance', which is the term used to describe a peak in the relative energy of the system's constituents. Such peaks can be attributed to transient aggregates, in which the lifetime is inversely proportional to the width of the peak. If energies could be measured that are suggestive of a resonance associated with matter comprising only neutrons, this would be one of the most noteworthy results in the past century of nuclear physics. Duer and colleagues' work indicates that the four-neutron system (a

tetraneutron) has an energy spectrum with a 'resonance-like' feature.

The authors undertook an experiment in which helium-8 nuclei (comprising two protons and six neutrons) were fired in a fast beam towards a stationary target of protons (Fig. 1a). The collision resulted in each helium-8 nucleus ejecting an  $\alpha$ -particle, which contains both protons but only two of the six neutrons, thus leaving behind four neutrons. The experiment did not detect these residual neutrons – instead, it detected the  $\alpha$ -particle and a proton emerging with equal and opposite momenta. The neutrons remained in the moving frame of the beam without recoiling from the collision. By measuring the energy of the  $\alpha$ -particle and proton, the team could attribute the missing energy to the four undetected neutrons. This energy provided a statistically unambiguous peak of the four missing neutrons that had a positive mean value, the classic signature of a resonance.

Duer *et al.* performed simulations suggesting that this peak was consistent with a resonance at 2.37 megaelectronvolts with a width of 1.75 megaelectronvolts, where both values have uncertainties of around 15%. This result is consistent with some previous work, but, statistically, it is far superior to other reported values (see, for example, ref. 2). The possibility that the observed peak could have resulted from processes other than  $\alpha$ -particle knockout (leaving an isolated tetraneutron) – for example, the ejection of two neutrons, followed by two more – was considered by the authors, and dismissed. However, the measured resonance was relatively wide, which can make it