Topological acoustics is therefore a promising research field that not only can produce phenomena that are difficult to realize in other physical systems, but could also bring about transformative technologies. ■

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50 Years Ago

The prospect of beer by the litre for British drinkers came a step closer last week. Mr Anthony Wedgwood Benn, the Minister of Technology, announced that the United Kingdom is to adopt the metric system of measurement by 1975 — the target date already accepted by British industry for its timetable … The industrial change is going ahead fast … but the non-industrial sector of the economy and the general public have been lagging behind … It is "imperative" for the planning of the change in the general sectors of the economy to be put in hand; if this is not done, "the dynamism of the industrial change will be lost" … The cost-effectiveness of metrication is not … likely to be known until it is a fact. So far, certainly, hunch has played a greater part than has sober analysis of the situation.
From *Nature* 3 August 1968

100 Years Ago

… Finally, there is the personal use of insecticidal preparations as aids to the primitive method of getting rid of [lice] — now referred to as "chat"-hunting … [T]he preparation should be of quick action and easy of application to clothing, and its issue should be as general and comprehensive as that of food … [P]astes are more economical and convenient than powders; fluids are out of the question. Crude "unwhizzed" naphthalene, produced by coke-oven plants, affords the most effective base, and may be conveniently mixed into paste form by the addition of soft soap or some grease, such as vaseline, in the proportion of 10 to 20 per cent … When it is necessary to use an anti-lice preparation on a hair-clad surface the use of vaseline, to which has been added ½ per cent. of veratrine dissolved in 5 per cent. of benzene, may be recommended.
From *Nature* 1 August 1918

METABOLISM

An unexpected trigger for calorie burning

The molecule succinate, which is a product of metabolism, promotes heat production and therefore calorie burning in brown fat in mice. This discovery could have implications for combating obesity in humans. SEE LETTER P.102

SHENG HUI & JOSHUA D. RABINOWITZ

There are two ways to lose weight: eat less to reduce the number of calories available for metabolism by the body, or burn more calories, for example through exercise. On page 102, Mills *et al.*[1] identify a molecule produced during nutrient metabolism that, surprisingly, induces calorie burning. This metabolite, succinate, activates energy expenditure in brown fat. Remarkably, supplementing the drinking water of mice with succinate can prevent the animals from gaining weight.

Brown fat is different from the white fat that builds up around our waistlines. Whereas white fat acts as an energy reserve, brown fat specializes in heat generation, and is essential for mammals to maintain their body temperature in the cold[2]. Brown-fat cells contain smaller lipid droplets than do white-fat cells, and have many more organelles called mitochondria[3], which enable brown fat to generate heat.

In mitochondria, a metabolic pathway called the TCA cycle breaks down nutrients such as glucose, lactate and fat into carbon dioxide, using the energy stored in the nutrients to generate high-energy electrons. These electrons are used to pump protons (hydrogen ions, H^+) out of the interior matrix of the mitochondrion into the space between the organelle's inner and outer membranes, thereby converting the energy into a proton gradient. Normally, protons re-enter the mitochondrial matrix through a membrane-spanning protein complex called the proton ATPase. This complex uses the energy stored in the proton gradient to convert ADP molecules into energy-carrying ATP molecules, and thereby generates most of the body's usable energy. But in brown fat, protons pass through another protein, uncoupling protein 1 (UCP1). This transporter uncouples the process of crossing the mitochondrial membrane from that of ATP production, effectively wasting the proton gradient's energy as heat (reviewed in ref. 4).

This capacity of brown fat to dissipate calories as heat has attracted much attention, in the hope of activating the process to combat obesity[5]. To do this, it is necessary to know what switches on calorie burning by brown fat. At the macroscopic level, the main answer is exposure to cold. At the mechanistic level, it has been proposed that the brain senses cold and sends signals to brown fat through a process mediated by proteins called β-adrenergic receptors[2]. But drugs that activate these receptors have not been successful in curbing obesity[6]. Thus, there is intense interest in finding new pathways that activate heat generation in brown fat.

Mills *et al.* began by searching for metabolites that are selectively abundant in brown fat, and whose concentration in this tissue increases during cold exposure. Their survey identified succinate, one of the metabolic intermediates of the TCA cycle.

The TCA cycle is generally assumed to be a cell-intrinsic process in which most intermediates are trapped in the mitochondrial matrix. Thus, most succinate is consumed by the same cell that produces it. Some succinate, however, makes its way into the bloodstream. The authors provide evidence that a key trigger for the release of succinate may be muscle activity, because shivering in response to cold increased blood succinate levels in mice.

To trace the fate of succinate circulating in

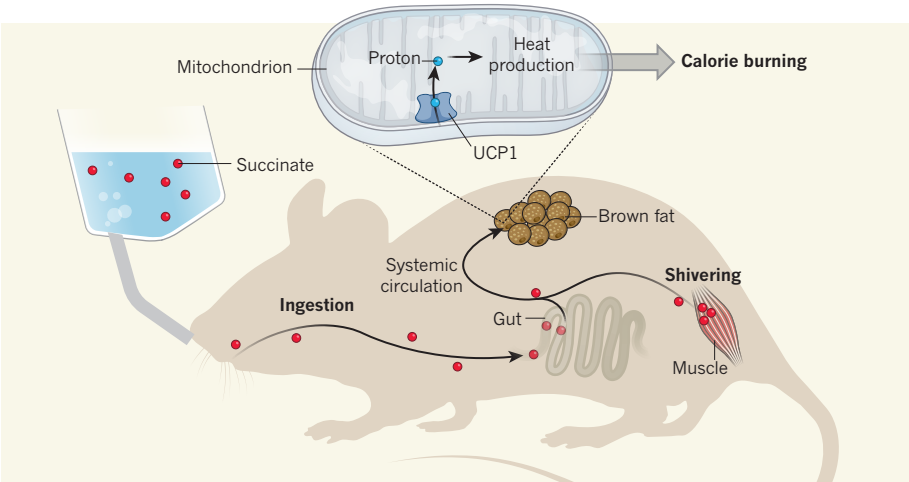

Figure 1 | Circulating succinate molecules mediate calorie burning. Mills *et al.*[1] report a mechanism by which weight gain can be controlled in mice. Succinate added to drinking water is ingested and enters the systemic blood circulation from the gut. Succinate is also released into the circulation by muscle cells during shivering in response to cold. From the circulation, succinate can enter brown-fat cells, which contain many organelles called mitochondria. Here, it triggers the mitochondrial protein UCP1 to leak protons (hydrogen ions; H^+), converting chemical energy into heat and thereby burning calories.

the blood, Mills and colleagues injected mice with succinate tagged by a heavy isotope of carbon. They found that the carbon isotope accumulated preferentially in brown fat. Thus, brown fat seems to be programmed to use circulating succinate as a fuel. Consistent with this, the authors showed that isolated brown-fat cells, but not most other cell types tested, avidly took up and burnt succinate.

Mills *et al.* next showed that acute succinate administration in mice raised the local temperature of brown fat. And, strikingly, administering succinate in drinking water for four weeks prevented obesity in mice on a high-fat diet. These metabolic effects depended on UCP1 — most of the beneficial metabolic effects of succinate were absent in mice genetically engineered to lack this protein. Thus, succinate activates heat production and calorie burning in brown fat (Fig. 1).

How exactly does succinate trigger heat production? In the TCA cycle, succinate is consumed by the enzyme succinate dehydrogenase. The activity of this enzyme produces molecules called reactive oxygen species (ROS), which have been proposed to promote heat generation by brown fat[7]. The authors therefore suggest that succinate accumulation induces calorie burning by increasing the activity of succinate dehydrogenase and so increasing ROS levels. However, it is unclear whether the contribution of circulating succinate to the TCA cycle in brown-fat cells is really sufficient to alter ROS levels and heat generation.

As an alternative explanation, perhaps succinate triggers a yet-to-be-discovered signalling system in brown fat. Or perhaps circulating succinate is sensed in a different part of the body, such as the brain, which then signals to brown fat to activate heat production. Defining the mechanism at work is of more than academic interest — it might prove important in determining the ideal dose and schedule for succinate administration in humans, or for identifying pharmacological alternatives to bulk succinate intake. Finding the molecular players involved will be crucial, the most obvious missing protein being the transporter that carries succinate into brown fat.

Humans, of course, differ from mice in many ways. One of the most obvious is our larger body size, which is associated with a lower ratio of body surface area to mass. As a consequence, we are better at staying warm than are mice, but worse at getting rid of heat. It is probably for these reasons that brown fat makes up a much lower percentage of our body mass[8]. Moreover, we lose brown fat as we age. This could limit the extent to which activation of metabolic processes in brown fat can alter calorie expenditure. Accordingly, methods to induce brown-fat properties in existing white fat might be needed as a complementary approach[5]. It will nevertheless be interesting to see whether succinate can induce substantial calorie burning in humans.

Taking a step back, circulating TCA intermediates have not previously been considered as key factors in metabolism. But several TCA intermediates are present in the circulation at substantial levels, and some of them, such as citrate, flow into and out of the bloodstream to a greater extent than does succinate[9]. The finding that circulating succinate has a well-defined, and perhaps even medically important, metabolic role raises the possibility that circulating TCA intermediates will more generally prove to be vital metabolic players. ■

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NEURODEVELOPMENT

Nascent neurons need nature and nurture

How genetic and environmental factors contribute to the generation of various subtypes of inhibitory neurons called interneurons in the brain is unclear. A study in mice provides new insight into this process.

CHRISTIAN MAYER & GORD FISHELL

The mature brain contains an enormous variety of locally projecting inhibitory neurons known as interneurons. How the brain's precise complement of interneurons is generated during development is a subject of lively debate. At its heart, this question is one of nature versus nurture. Young interneurons are 'born' in a region called the subpallium and undergo a long migration to reach their final positions in the brain's cortex — but it remains unclear how much of an interneuron's mature fate is bestowed by its genetic identity, which is established when the cell stops proliferating, and how much is acquired through nurture during migration. Writing in *Nature Neuroscience*, Lim *et al.*[1] investigate how migration influences cellular identity.

There is evidence to support roles for both nature and nurture in defining the identities of the different classes, types and subtypes of