From the archive

An engaging physics textbook, and diary gossip suggests that Shakespeare died of a fever after revelling with playwrights.

100 years ago

Readable School Physics. By J. A. Cochrane — A teacher who loves his subject will find matter of interest for his pupils even in its most prosaic parts. "This book," writes Mr. Cochrane in an interesting Preface, "is an attempt to humanise Elementary Physics without popularising it." We are of opinion that in this task the author has achieved very considerable success. Theory has been given the main prominence. Experiments have not been described unless to elucidate principles. References to the makers of scientific history are frequent, and are reinforced by a number of interesting plates which include portraits of Newton, Pascal, Boyle, Galileo, and Joseph Black. The pupil's own experience is brought into connexion with physical principles as often as possible. Part I, which might have been called Mechanics instead of Hydrostatics since it includes chapters on volume, weight, and density (not to mention surveying), occupies about two-thirds of the book, the remainder being devoted to what is certainly a "readable" account of the elementary principles of heat.

From *Nature* 9 September 1922

150 years ago

Rev. John Ward ... was Vicar of Stratford-upon-Avon, from 1662 till his death in 1681. He was a man of general knowledge, and was specially skilled in the diseases of women and children. It is not known that he obtained the archiepiscopal licence to practise physic, but he certainly practised the healing art ... His diary, 1648–1679, is sensible and entertaining. It is chiefly known as containing a notice of Shakespeare, with the only extant account of the cause of his death ... "a feavour" caused by a carouse with Drayton and Ben Jonson. The Diary is in the Library of the Medical Society of London. It was edited by Dr. Charles Severn, and published by Colburn, in 1839.

From *Nature* 5 September 1872

Metabolism

Inosine molecules fire up weight loss

Katrien De Bock & Christian Wolfrum

Brown fat in the body converts energy into heat. The discovery that inosine molecules are released from dying brown fat and induce heat production in nearby brown fat cells could point to a way of combating obesity. **See p.361**

Almost 60% of adults and nearly one-third of children in Europe are overweight or obese (see go.nature.com/3bsIjrd). Beyond lifestyle interventions, effective therapies to reduce obesity mostly involve surgery, so new, less-invasive strategies are required. A type of fat known as brown adipose tissue (BAT) is currently the subject of interest as a target for weight-loss intervention, because it burns calories by releasing stored energy in organelles called mitochondria and converting it to heat — a process called thermogenesis[1,2]. Evidence indicates that the activity of BAT is associated with reduced weight and improved metabolic health[1]. On page 361, Niemann *et al.*[3] outline a previously unknown regulatory pathway governing the activity of BAT that could potentially be targeted for therapeutic weight loss.

The authors first housed mice at thermoneutral temperatures (the ambient temperatures at which body temperature can be maintained without the need to expend energy). This inactivates fat cells in BAT called brown adipocytes and triggers their death through a process known as apoptosis. Niemann and colleagues observed that apoptosis led to the formation and activation of nearby brown adipocytes; these could originate from a different type of fat cell called a white adipocyte, or from precursors of brown and white adipocytes. The new brown adipocytes therefore effectively replace the dying population.

Niemann *et al.* next asked what signals are being released from the dying BAT to cause this effect. Analysis of the dying cells revealed that, among more than 300 metabolic products released during apoptosis, specific molecules called purines were the most abundant. The researchers tested the ability of three purines to trigger the activation of BAT and identified one, inosine, as the probable major effector.

The authors found that inosine acts by binding to either of two purine receptor proteins — A_{2A} and A_{2B} — on the surface of the neighbouring cells. This activates a signalling pathway known as the PKA–cAMP cascade, which induces brown adipocyte formation and activation. The researchers also demonstrated that administering inosine to obese mice increased BAT activity and overall energy expenditure, and even induced weight loss.

To further dissect this pathway, Niemann and colleagues investigated how extracellular inosine concentration is regulated by transporter proteins that shuttle inosine across the cell membrane into existing brown adipocytes. They showed that the protein Ent1 is a prominent regulator of inosine uptake. They therefore genetically engineered mice to lack Ent1 in adipocytes, and found that the animals showed enhanced extracellular inosine levels, greater BAT activation and higher overall energy expenditure compared with control animals. Accordingly, administration of a drug called dipyridamole, which inhibits Ent1, enhanced BAT activity and energy expenditure in wild-type mice. Most importantly, a genetic analysis in humans indicated that a particular variant of ENT1 (Ile216Thr) is associated with lower weight and better metabolic health than is seen in people who do not have this variant.

Together, the results indicate that the shuttling of inosine into cells by Ent1 limits the pool of extracellular inosine available to brown adipocytes, maintaining the overall number of thermogenic adipocytes. When the cells die, the release of inosine acts as a 'replace me' signal, causing increased formation and activation of brown adipocytes, and a concomitant increase in energy expenditure (Fig. 1).

Until now, little has been known about the maintenance of thermogenic adipose tissue and regulation of its overall abundance under normal conditions, or its contribution to energy metabolism. Removal of brown adipose tissue in mice has been shown[4] to trigger the formation of thermogenic adipocytes in other parts of the body, suggesting that the organism can indeed control the overall number of these cells. Inosine might be one signal that mediates this brown adipocyte formation in response to environmental factors.

Given the seriousness of the obesity

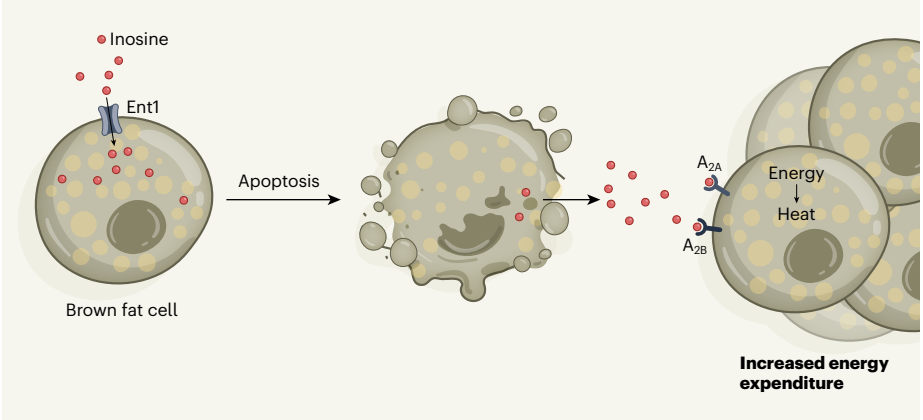

Figure 1 | A regulatory pathway in brown adipose tissue (BAT). Brown fat cells convert energy to heat. Niemann *et al.*[3] provide evidence that this process, known as thermogenesis, is regulated by the molecule inosine. Levels of extracellular inosine are maintained in normal BAT by the protein Ent1, which transports inosine into brown fat cells. But if the cells die through apoptosis — as occurs when they are moved from cold to warm conditions — the inosine is released. It binds to A_{2A} and A_{2B} receptor proteins on neighbouring cells, triggering the formation of new brown fat cells (not shown) and activating thermogenesis, thus increasing energy expenditure.

pandemic, it is essential to discover new strategies to induce weight loss. One potential branch of therapies involves small gut molecules such as GLP1, which drive weight loss mainly by restricting energy intake[5]. But a concern is that this restriction could be compensated for by a reduction in overall energy homeostasis. In this context, the action of molecules that modulate BAT function have gained prominence. Indeed, several molecules have already been shown to control the activity of BAT[6,7]. Now inosine enters the stage.

The fact that the pathway uncovered by Niemann *et al.* has a rapid response time (15 minutes) makes it highly versatile as a drug target. But it also means that the pathway must presumably be tightly regulated, to keep a lid on energy expenditure. The substantial expression of Ent1 that the authors observed indeed suggests that inosine uptake might be crucial to maintaining energy expenditure at normal levels. The pathway could play into a person's basal metabolic rate (the number of calories burnt performing life-sustaining functions), which varies widely between individuals[8]. Perhaps certain mutations in the *ENT1* gene predispose people to have a higher basal energy expenditure. Whether people with the reported Ile216Thr mutation derive their metabolic benefits from an increase in basal metabolic rate is a key question for future studies.

Another question is whether the effects of inosine are exclusively mediated by signalling through A_{2A} and A_{2B}, or partly result from intracellular changes in inosine content caused by Ent1-induced uptake, where inosine could act as a precursor for the synthesis of metabolic compounds[9], rather than as a signalling molecule. Similarly, it should be noted that Ent1 transports other compounds, too. Although Niemann and colleagues' data suggest that inosine is the main regulator of BAT induction, the possibility cannot be excluded that other Ent1 substrates are activators of A_{2A} and A_{2B}.

Inosine might also have immune modulatory effects in BAT that play into the weight-loss pathway. It has been shown to have immunosuppressive properties in several other cell types[10]. Furthermore, Niemann *et al.* found that ultraviolet irradiation triggers the release of inosine from endothelial cells, which line blood vessels in BAT. Inosine might therefore affect the microenvironment of BAT in multiple ways, thereby indirectly influencing tissue function.

Finally, before considering how this pathway could be harnessed to treat obesity, some key concerns should be addressed. First and foremost, BAT activation is driven by the sympathetic nervous system, which also increases heart rate and blood pressure, two factors linked to the risk of cardiovascular disease. In addition, A_{2A} activation in the heart increases the basal heart rate[11]. Furthermore, inosine is a precursor of urate, which has been implicated in the development of gout and rheumatoid arthritis — well-documented co-morbidities of obesity. Mitigating these risks will be essential if inosine-mediated BAT activation is to be used safely to combat obesity.

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Chemistry

Synergistic active sites observed in a solid catalyst

Tiefeng Wang

A solid catalyst has been prepared in which pairs of active sites work synergistically to promote an industrial chemical reaction, and the mechanism has been determined — a breakthrough for 'pair site' catalysis. **See p.287**

More than 80% of globally produced chemicals are made using solid catalysts[1], which are easy to separate from products formed in fluid states — a key practical advantage that lowers manufacturing costs. The improvement in solid catalysts (known in the field as heterogeneous catalysts) is therefore a dominant theme in academic and industrial-chemistry research. However, some important industrial processes still use soluble (homogeneous) catalysts, because the best available heterogeneous catalysts do not promote the formation of the desired products with sufficiently high selectivity for commercial applications[2]. On page 287, Ro *et al.*[3] report a solid catalyst that might change this situation for a widely used industrial process: the reaction of ethylene (CH_2=CH_2) with hydrogen and carbon monoxide to produce propanal (CH_3CH_2CHO), a process known as hydroformylation. More broadly, the findings herald a new era of research into a class of heterogeneous catalysts known as pair-site catalysts, in which different