METABOLISM

Bile acids heat things up

John D. Baxter and Paul Webb

Thyroid hormone causes fat loss, but harnessing this action to treat obesity is difficult because it is associated with harmful side effects. However, bile acids generate active thyroid hormone just where it is needed.

Obesity is pandemic in the Western world and is becoming a problem in other countries[1]. Stroke, heart attack, diabetes, kidney failure, arthritis and peripheral vascular disease are all consequences of this disorder. But the outlook is not all bleak. If obesity can be reduced, there should be enormous health benefits — even a 5% decrease in body weight through diet and exercise cuts the risk of type 2 diabetes by more than 50%[2]. Nevertheless, efforts to address the problem by encouraging lifestyle modifications have met with limited success. So major efforts are under way to find other therapies. In this issue, Watanabe *et al.* (page 484)[3] report a previously unappreciated role for bile acids in regulating fat that might also be exploited pharmacologically to tackle obesity.

Body-weight control is essentially a question of energy balance: if we eat more calories than we expend, we become fat[4]. Many therapies, therefore, aim to reduce food intake. Surgery has had impressive results, but carries substantial risks. Current pharmacological manipulation of the pathways that regulate appetite or block dietary fat absorption have limited utility. High-fat, fast-food diets can override delicate regulatory networks established by appetite-regulating hormones, and it has been difficult to develop drugs that reduce food intake in the face of powerful environmental influences. Moreover, drugs that block fat absorption have limited efficacy.

Are there other approaches to combat obesity? Endocrinologists have long known that hormones can alter the body's fat content. And although they cannot override the laws of thermodynamics, hormones do alter the energy-balance equation by increasing metabolic rate. An illustration of this principle is seen in disorders involving excess thyroid hormone, where stimulation of metabolic rate and decrease in body fat can occur even with increased dietary intake. Thyroid hormone itself cannot be used to treat obesity because of deleterious side effects that can include increased heart rate, atrial arrhythmias and breakdown of muscle and bone. But manipulating this pathway may be useful, and selective analogues of thyroid hormone are already showing promise in reducing body fat in animals[5].

Watanabe *et al.*[3] now report that bile acids have a role in regulating thyroid hormone signalling and energy homeostasis. Although the classical role for bile acids is to enhance fat absorption in the intestine, they also regulate the metabolism of fat by acting as signalling molecules through pathways involving the cell-surface receptor TGR5 (ref. 6) and nuclear receptors such as FXR (ref. 7). Watanabe *et al.* show that bile acids, which include cholic acid, stimulate production of active thyroid hormone in fat cells (Fig. 1).

Bile acids have been shown to mitigate diet-induced obesity, but this work[8] has received limited attention. Watanabe *et al.* confirm and expand this observation, showing that feeding mice with cholic acid moderates the effects of a high-fat diet. The animals were less obese and their blood glucose levels were better regulated than in controls fed the high-fat diet alone. Cholic acid had no effect on body weight in lean animals, and mice fed cholic acid did not eat less. Instead, bile acids reduced weight gain by increasing energy expenditure: the treated mice consumed more oxygen and produced more carbon dioxide, and so had a decreased respiratory quotient, indicative of increased fat burning.

The basis for this remarkable effect became clear through genomics. Large-scale gene-expression studies showed that bile acids increase the expression of several genes involved in energy metabolism in brown fat tissue but not in liver. One of these genes encodes the type 2 deiodinase enzyme (D2), which converts the minimally active precursor of thyroid hormone, thyroxine (T_4), into the

TRAVEL

Fitting the bill

Anecdotal evidence about human travel is plentiful. But quantifying human movement and dispersal, and then applying general principles to those data, is not straightforward. Elsewhere in this issue, a group of theoretical physicists describe how they have taken an ingenious approach to the problem (D. Brockmann *et al. Nature* **439,** 462–465; 2006). They use the dispersal of dollar bills within the United States as a proxy measurement for human movement.

The researchers analysed data on the peregrinations of more than half-a-million US dollar bills recorded over a five-year period on an online bill-tracking system (www.wheresgeorge.com). This allowed them to quantify even statistically rare events with high reliability. They found that the movement of dollar bills resembles enhanced diffusion, or 'superdiffusion'. Long-distance jumps are disproportionately important in the distribution of travelling distances. And this distribution decays as a power law reminiscent of 'Lévy flights', which are characterized by many short steps interspersed with long-distance jumps.

The result may seem unsurprising — most cash transactions are carried out locally, but every now and again someone departs and uses the bill at a distant location. The beauty is that actual numbers can now be put on the process.

Although the observed distribution of travelling distances implies superdiffusion, however, this process is attenuated by the tendency of bills to remain in the same area for longer than might be expected given the overall pattern of movement. Thus, human travelling behaviour apparently involves disproportionately long waiting times between displacements as well as jumps without any characteristic distance scale.

PARAMOUNT/THE KOBAL COLLECTION

But how well do bill trajectories reflect actual human movement? Happily, the authors find that data on passenger travel on the US aviation network, and long-distance human travel information published by the US Bureau of Transportation Statistics, agree well with the results based on dollar-bill trajectories.

This research is more than a curiosity — epidemiologists could in principle use quantitative information on human movement to understand better how infectious diseases such as influenza spread.

Rory Howlett

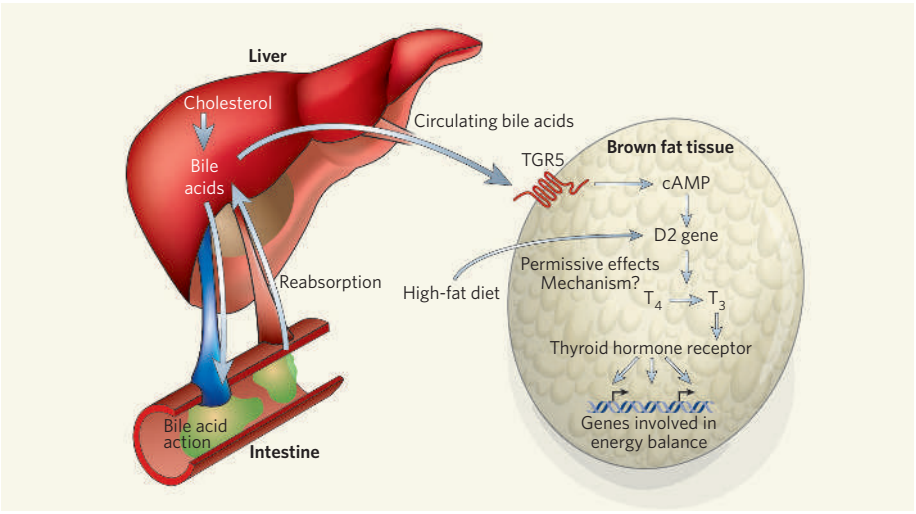

Figure 1 | Bile acids in energy homeostasis. Bile acids are synthesized from cholesterol in the liver, stored in the gallbladder, and secreted after meals to promote absorption of fat from the intestine. They are then either excreted or reabsorbed into the circulation. Watanabe *et al.*[3] demonstrate that bile acids increase the metabolic rate in fat cells by binding to a G-coupled protein receptor (TGR5) that increases cAMP content and induces D2 expression, thereby enhancing local conversion of T_4 to the active T_3. These effects are observed only in animals that are fed a high-fat diet, as this sensitizes the D2 response to bile acids through an unknown mechanism.

potent form, triiodothyronine (T_3). Direct evidence that D2 (and therefore T_3) is involved in the actions of cholic acid came from mice in which the D2 gene had been disrupted, and which showed none of the effects seen in animals fed cholic acid. Increased metabolic rate in the brown fat of rodents through D2-induced increases in T_3 is crucial for sustaining body temperature in cold conditions (adaptive thermogenesis). So bile acids seem to block fat accumulation by inducing thyroid hormone signalling in brown fat.

Watanabe *et al.* have begun to tease apart the mechanism behind the effects of D2 on cholic acid. They show that bile acids regulate D2 expression by binding to TGR5, which is present in high levels in brown fat, and rule out the possibility that FXR is involved. TGR5 belongs to a family of receptors known as G-protein-coupled receptors. It increases intracellular cyclic AMP (cAMP), which is already known to increase D2 levels. The authors may also have explained why the bile-acid effect is seen in obese and not lean animals: the induction of D2 in the brown fat from mice on the high-fat diet was more sensitive to activators of the cAMP pathway than in controls. However, the origin of this sensitivity is unclear.

Is this discovery relevant for humans? The tissues involved in thermogenesis are different in humans and rodents: adult humans have very little brown fat, but skeletal muscle is crucial for energy homeostasis. Human skeletal muscle expresses significant levels of D2, and Watanabe *et al.* detected TGR5 in cultured human skeletal muscle cells. Treatment with bile acid increased metabolic rate in these cultures. The authors note that a human variant of the D2 gene is associated with a decreased rate of whole-body glucose disposal, a rate that is mostly determined by glucose uptake into muscle. So there are hints that D2 regulates metabolism in skeletal muscle in humans in a similar manner to that in brown fat in mice.

The bile-acid pathway might be important from both physiological and pharmacological perspectives. Postprandial concentrations of bile acids should be sufficient to stimulate cAMP production and D2. So bile acids could be hormonal signals linking food intake to diet-induced increases in metabolic rate. Bile acids caused toxic side effects, especially in the liver, when they were tested in other disorders[9], so any similar compounds designed for clinical use would need get around these problems. However, the finding that bile acids increase T_3 levels selectively in tissues where T_3 can promote energy expenditure provides a significant advance in our understanding of the regulation of energy homeostasis and a potential approach to fighting obesity. ■

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50 YEARS AGO

Among the strangest forms of animal behaviour is that of the honey-guides, African birds distantly related to the American woodpeckers, which 'guide' men, baboons and ratels (honey-badgers) to the nests of wild honeybees—supposedly so that these nests can be broken open. A study of the behaviour is described by Dr. Herbert Friedmann, U.S. National Museum curator of birds, in a bulletin issued by the Smithsonian Institution, Washington... "When the bird is ready to begin guiding, it either comes to the person and starts a repetitive series of churring notes or it stays where it begins calling these notes and waits for the human to approach it more closely... As the person comes to within 15 to 50 feet from it, the bird flies off with an initial conspicuous downward dip, and then goes off to another tree, not necessarily in sight of the follower; it is more often out of sight than not. It waits there, churring loudly until the follower again nears it, when the action is repeated. This goes on until the vicinity of the bees' nest is reached... It waits for the follower to open the hive and usually remains until the person has departed with a collection of honeycomb, when it comes down to the plundered nest and begins to feed on the bits of comb left strewn about."
From *Nature* 28 January 1956.

100 YEARS AGO

"Sounding Stones" — It may be of interest to add to the list of musical stones provided by your correspondents another limestone, viz. the very hard, crystallized, coral rock of the coasts of British East Africa. Among the bizarre forms assumed by these rocks under the erosion of the sea, isolated pillars with projecting arm at the top, like a gallows or an inverted capital "L," are common in places. This horizontal arm in many cases gives a clear musical note when struck with a stone or hammer, being thus a ready suspended natural gong.
From *Nature* 25 January 1906.

50 & 100 YEARS AGO