METABOLISM

Bile acids heat things up

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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.

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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.

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