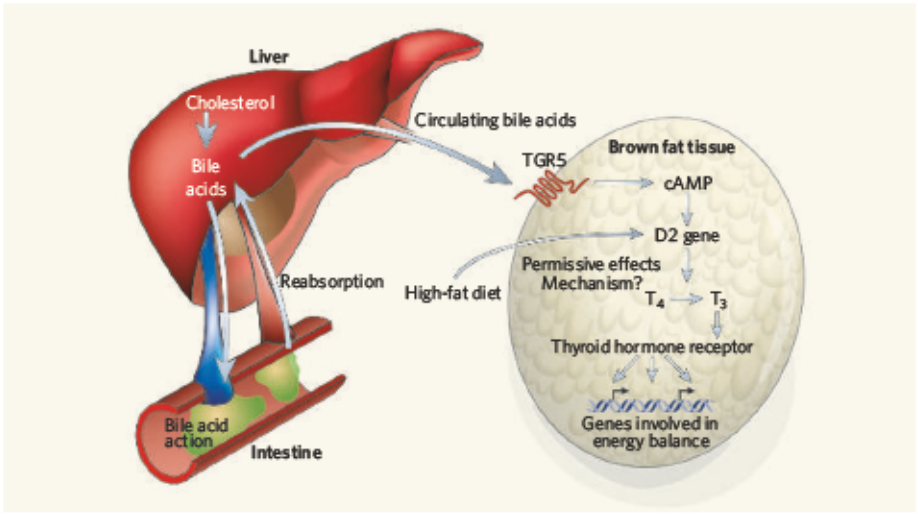

Figure 1 | Bile acids in energy homeostasis. Bile acids are synthesized from cholesterol in the liver, stored in the gallbladder, and secreted after meals to promote absorption of fat from the intestine. They are then either excreted or reabsorbed into the circulation. Watanabe *et al.*[3] demonstrate 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