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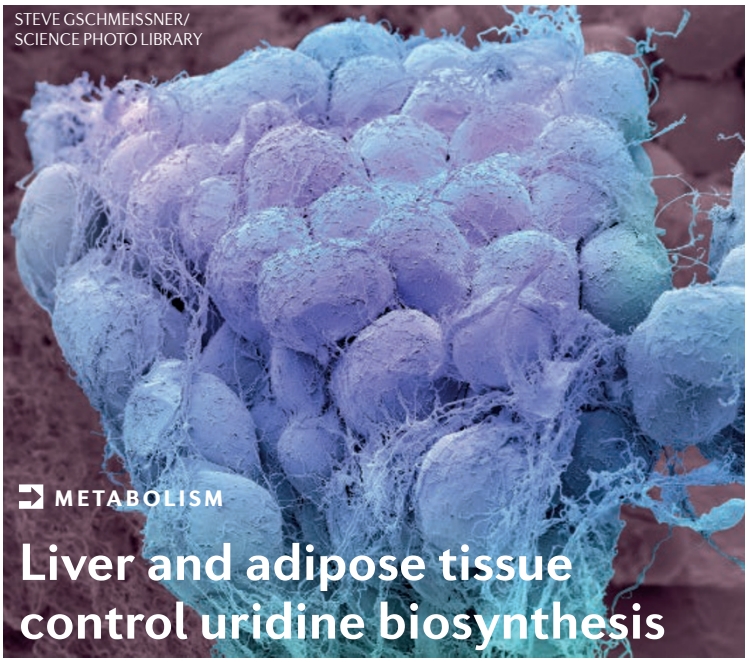

METABOLISM

Liver and adipose tissue control uridine biosynthesis

> "…adipose tissue is an important source of uridine"

Uridine is an essential component of a range of cellular functions and is required for cell survival. New research has now identified an adipo–biliary–uridine axis that seems to be involved in regulating energy homeostasis.

"We were fascinated for the past couple of years by the massive metabolic changes that have to take place in the liver and adipose tissue during feeding–refeeding cycles," says lead author Philipp Scherer. This interest led the group to study uridine in mice, rats and humans.

Measurements in rodents and humans revealed that plasma levels of uridine change during fasting and refeeding. In C57BL/6 mice, levels of uridine in plasma doubled after 24 h of fasting, returning to basal levels within 4 h of refeeding. Similar results were seen in rats, but the return to basal levels took 24 h. In healthy humans, levels of uridine were 4.63 ± 0.75 μM after an overnight fast and then dropped to 1.84 ± 0.44 μM 4 h after a meal. By examining the bile of wild-type mice, the investigators were able to demonstrate that the excess uridine was cleared through the biliary system.

Body temperature is known to drop during fasting (to reduce the metabolic rate) and increase after a meal. To determine whether uridine was involved in this thermoregulation, the investigators injected mice with 1,000 mg/kg of uridine. The body temperature of the mice dropped rapidly after the injection, from 37.9 ± 0.9 °C at baseline to 34.0 ± 1.6 °C at 30 min. These findings suggest that uridine is a driving force of thermoregulation during fasting–refeeding.

Uridine also seems to influence glucose tolerance. Wild-type mice on a high-fat diet and *ob/ob* mice were given an oral dose of glucose and uridine, which resulted in improved glucose tolerance in the wild-type mice but not in the *ob/ob* mice. After an intraperitoneal injection of uridine, glucose tolerance improved in wild-type mice on a high-fat diet and deteriorated in *ob/ob* mice. These results suggest that leptin could mediate the effects of uridine on glucose homeostasis.

Interestingly, although the liver has been thought to be the primary organ for uridine biosynthesis, Scherer and colleagues found that the genes that encode the proteins involved in uridine biosynthesis are downregulated in the rodent liver during fasting. By contrast, *Cad* (which encodes the rate-limiting enzyme in uridine biosynthesis) was upregulated in three adipose depots, which suggests that adipose tissue is an important source of uridine. "Liver and adipose tissue take turns in uridine synthesis responsibilities," explains Scherer. "In the fed state, the healthy liver shuts down glucose production and produces uridine; in the fasted state, adipocytes produce uridine, allowing the liver to focus on glucose production."

These findings have opened up several avenues of research, which Scherer and his team are planning to investigate. The current paper included healthy humans, so whether these effects are also seen in patients with diabetes mellitus needs to be established. Whether uridine influences glucose tolerance in humans also needs to be determined. "Can we prompt adipocytes to chronically overproduce uridine, thereby prompting a 'futile' biosynthetic reaction that consumes calories?" asks Scherer. "In contrast to uncoupling of mitochondria that also wastes energy, but can lead to overheating, chronic overproduction of uridine might not have any negative consequences." However, further research is needed to demonstrate that overproduction of uridine is not harmful. "We propose to follow the conceptual approach of SGLT2 inhibitors that 'waste' glucose in urine, but focus on uridine rather than glucose," concludes Scherer.

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