METABOLISM

Fat controls U

Circulating uridine acts as a hunger signal

By **Martin Jastroch**[1,2] *and* **Matthias H. Tschöp**[1,2,3]

Uridine (U) is a remarkably important molecule that is essential for a number of evolutionary and biological processes. It consists of the pyrimidine-analog uracil, which is linked to a ribose sugar. Uracil itself can be formed abiotically from pyrimidine, suggesting that this base is a central building block of life. Uridine, by contrast, is a precursor for RNA, thus linking genetic information to the expression of proteins. Importantly, when phosphorylated to uridine triphosphate (UTP), it activates glucose to synthesize glycogen stores and thereby controls glucose metabolism. Uridine also has been implicated in neuron functions and brain processes. On page 1173 of this issue, Deng *et al.* (*1*) offer transformative insights into the systemic regulation of circulating uridine and its actions in mammals, with implications for the potential of therapeutic uridine supplementation in general and new precision treatments of metabolic diseases in particular.

Uridine's base uracil is one of five building blocks required for the production of DNA and RNA. In the past few years, uracil has received attention in studies looking at the origin of life and mechanisms of evolution (*2*). Indeed, uracil can be formed without the involvement of living organisms (*2*). This process starts with pyrimidine, which can be found on meteorites, fostering the "panspermia" hypothesis—that pivotal organic molecules exist in space with the potential of sparking life beyond our planet (*3*). At the beginning of life, uracil may have catalyzed several of the first few chemical reactions, and the "memory" of these reactions likely has been subsequently incorporated in the form of DNA-like structures. Presumably, uracil was soon methylated, forming thymine, to achieve greater stability in the DNA. In RNA, a more dynamically regulated molecule, uracil remains the base that pairs with adenosine, as stability is not critical for short-lived molecules such as RNA. Indeed, molecules with low chemical stability are advantageous for dynamic processes, and evolution has repeatedly utilized those labile molecules to rapidly respond to environmental cues. To sustain life in a changing environment, e.g., in response to nutrient shortage, it is essential to adjust metabolic processes to maintain cellular homeostasis. This principle has applied throughout evolution, as evidenced by the incorporation of ancient molecules into new biological pathways. Therefore, it may also be feasible to link a small molecule such as uridine to the control of metabolic plasticity and homeostasis.

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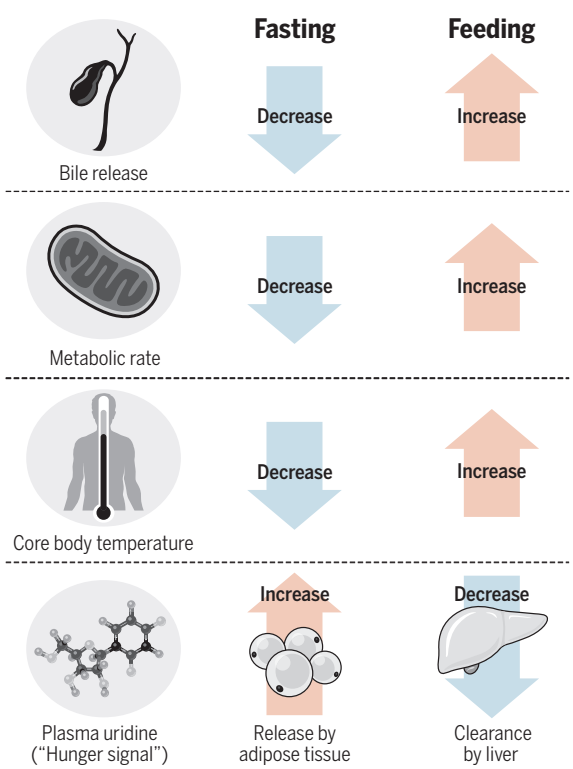
The metabolic effects of nucleosides have been mostly focused on uridine's sister molecule, adenosine, presumably because of the latter's striking impact on metabolism. Furthermore, dietary supplementation with uridine does not markedly alter plasma concentrations of this nucleoside, and the liver effectively breaks down dietary uridine (*4*). Yeast would theoretically offer a uridine-rich source, but plasma increases of uridine after beer consumption may also be explained by the influence of alcohol on liver metabolism (*5*).

Deng *et al.* discovered that uridine concentrations in blood are affected predominantly by nutritional status in rodents and humans, in particular by fasting and (re)feeding. They suggest that plasma uridine concentrations directly affect how many calories are being burned in thermogenesis-related processes (which affects core body temperature), as shown by correlative cues and by pharmacological intervention or administration of uridine. The authors dissected how the liver, gallbladder, and adipose tissue synergize to calibrate plasma concentrations of uridine in a mouse model. Intriguingly, there appears to be some functional interaction with leptin, an adipose tissue hormone that regulates energy balance by inhibiting hunger. The Deng *et al.* study shows that leptin may even mediate some of the effects of uridine. The authors further observed that bile is another key determinant of plasma uridine concentration by comparing how orally versus intravenously supplied uridine differentially affects plasma uridine concentrations. Examining specific murine loss-of-function models, including targeted adipocyte ablation, disruption of adipocyte function in general, and abrogation of uridine biosynthesis specifically, the authors determined that adipose tissue is a major contributor of uridine synthesis and excretion.

Although the findings of Deng *et al.* are paradigm shifting, as they identify circulating uridine as a novel link between systemic nutrient availability, adipocyte function, and cellular energy homeostasis, they also raise many questions. It remains to be clarified, for example, how exactly uridine mechanistically exerts changes in mammalian metabolism. Also, testing and validating other potentially contributing mechanisms, including how and where the interaction with leptin signaling occurs, will certainly be a subject of future studies. Interestingly, uridine

Hunger signal

Circulating uridine links nutrient availability, adipocyte function, and cellular energy homeostasis. Adipose tissue is a major source of uridine that is released into the blood in response to fasting.



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diphosphate (UDP) mediates changes in appetite by activating purinergic P2Y6 receptors on hypothalamic neurons that release Agouti-related protein, a potent appetite stimulator. These neurons belong to a brain circuitry that controls systemic metabolism (*6*). This effect of UDP likely offers a glimpse into the complexity of how changing uridine plasma concentrations may differentially affect metabolic homeostasis in an organ-specific manner.

Metabolic studies on uridine, its regulation, and the effects on energy metabolism are particularly intriguing in the light of how mammals respond to food shortage. A uridine-induced reduction in body temperature would save energy, and promotion of glucose uptake by cells may help to overcome cellular energy deficits. Uridine may act in a way similar to that of a small-molecule hunger signal. Although uridine supplements appear to have no effects because they are excreted in bile, this clearance system appears to be not fully developed in human infants, where uridine monophosphates enriched in mother's milk can enter into and potentially control the infant's metabolism (*7*). In this situation, uridine may act as a nutrient-derived hormone ("nutrikine").

This discovery of uridine's physiological roles in maintaining systemic metabolic balance is undoubtedly of fundamental and broad importance to biology and medicine. Plasma uridine controls dietary responses and modulates leptin signaling, thereby governing glucose and insulin sensitivity. Specifically, targeting UDP signaling may offer intriguing potential for treating the metabolic disease states characterized by adiposity, impaired glucose tolerance, and hypercholesterinemia. Tissue-specific approaches could include the hypothalamic inhibition of the P2Y6 receptor to mitigate food intake and to improve systemic insulin sensitivity (*8*).

If uridine can help to reverse the worldwide obesity and diabetes pandemic, this fifth base will surely take center stage in metabolism research. ■

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NANOSCALE TRANSPORT

Probing the limits of heat flow

Studies of atomic point contacts reveal the fundamental quantum of heat transport

By **Dvira Segal**

The existence of universal upper bounds (limits) for the rates of transport of electricity and thermal energy is a striking manifestation of quantum mechanics. These fundamental bounds can be revealed in low-dimensional constrictions defining a single transport channel. The discrete unit (quantum) of electrical conductance G_0 has been observed in many experiments dating back to 1988 (*1, 2*), but the quantum of thermal conductance $G_{0,\mathrm{Th}}$ has been much more challenging to probe. Unlike tiny electrical currents, it is much harder to measure minute heat currents in a reproducible manner. On page 1192 of this issue, Cui *et al.* (*3*) conquer this challenge by developing an experimental platform for studying quantum thermal transport at the atomic limit. Their work reveals that thermal conductance can be quantized even at room temperature, as well as the fundamental relation between the thermal and electrical conductances. This study paves the way for investigations of thermal phenomena in individual molecular devices, with technological ramifications for controlling energy transport in nanoscale electronic circuitry.

The Landauer theory (*4*) describes transport of wavelike electrons. It predicts that the electrical conductance (the inverse of resistance) of perfect channels is given by $G_0 = 2e^2/h$, where e is the electron charge and h is Planck's constant (the factor of 2 accounts for spin-up and spin-down electrons). This value, an upper bound for the electrical conductance of a single channel, only depends on fundamental constants. Thermal conductance is quantized in the basic unit of $G_{0,\mathrm{Th}} = \pi^2 k_B^2 T/(3h)$, where k_B is Boltzmann's constant and T is temperature. This value represents the maximum rate at which thermal energy can be transported through a single channel and is truly universal. It is indifferent to the material properties and the type (statistics) of energy carriers, and has been verified experimentally for transport by phonons (*5*), photons (*6–8*), and electrons (*9, 10*).

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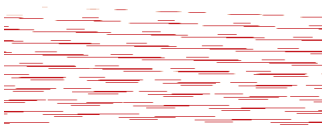
It is evident from the above that the thermal conductance quantum is related to the electrical conductance quantum by fundamental constants and temperature, but this relation is valid more generally and in radically distinct scenarios. First, for phase-coherent quantum transport (possibly through multiple and imperfect channels), Landauer theory asserts that the electronic contribution to the thermal conductance $G_{\mathrm{Th,e}}$ relates to the electrical conductance G_e as $G_{\mathrm{Th,e}} = TL_0G_e$, where $L_0 = (\pi^2/3)(k_B/e)^2$ is the Lorenz number. This relation holds so long as the electronic transmission function across the constriction only varies weakly with energy in the relevant range (around the Fermi energy), on the scale of the thermal energy k_BT.

Nevertheless, it is intriguing to recall that macroscopic, classical (ohmic) metal wires follow the same relation, originally put forward in 1853, in an empirical form. This Wiedemann-Franz law can thus be observed in different situations, whether transport is governed by quantum or classical principles. Its assessment, and possibly invalidation, can reveal microscopic details about transport, such as which coherent regime dominates charge transport in a given system, or if many-body interactions are influential or the noninteracting-electron model holds.

"Probing the quantum of thermal transport in atomic junctions requires exceptional thermal sensitivity, stability, and reproducibility..."

To address basic questions in electronic thermal transport at the nanoscale, measurements in the ultimate microscopic limit are required. Cui *et al.* report on an experimental setup with precise and decisive measurements of the thermal conductance of single-atom junctions, with the quantum of conductance observed at room temperature. By studying the electrical and thermal conductances of both gold (Au) and platinum (Pt) junctions concurrently,



Editor's Summary

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