neurons are actively lowering body temperature, other non-QRFP preoptic neurons could continue to regulate body temperature, but at a lower level.

Takahashi *et al.* showed that nearly 80% of the QRFP neurons expressed Vglut2 but not Vgat. By contrast, only about 7% expressed Vgat but not Vglut2, and around 13% expressed both. Deleting Vgat from the QRFP neurons slightly slowed the initial fall in body temperature caused by activating these cells, but body temperature reached a level comparable to that of control animals after six hours. Deleting Vglut2, by contrast, prevented a hibernation-like state. Thus, the hypothermia produced by QRFP neurons is predominantly mediated by glutamatergic transmission.

Previous research has indicated that many of the preoptic neurons that drive hypothermia express proteins called pituitary adenylate cyclase-activating peptide (PACAP) and brain-derived neurotrophic factor (BDNF)[7]. Takahashi and co-workers demonstrated that most preoptic QRFP-expressing neurons also expressed BDNF and PACAP. However, about 75% of the BDNF and PACAP neurons in the median preoptic nucleus did not express QRFP. Similarly, 75% of the QRFP neurons expressed the EP3 receptor, but many EP3-expressing neurons did not express QRFP.

Hrvatin and co-workers used a different approach. The group analysed a marker of neuronal activity to determine the neuronal populations activated during torpor caused by 24 hours of food deprivation. The active neurons were distributed similarly to QRFP cells, and many of them expressed PACAP. Thus, the results of the two studies, taking very different approaches, reinforce one another.

Taken together, these observations suggest that there are several subpopulations of thermoregulatory neurons clustered together in the median preoptic nucleus, each distinguished by a unique pattern of gene expression. Among these, the QRFP group seems to be particularly important for producing deep hypothermia. This process is necessary when animals do not have sufficient food available to maintain their typical levels of metabolism and activity. At such times, animals can undergo daily torpor (brief periods when their body temperature might drop to 30° C or lower for a few hours, frequently seen in mice and rats) or hibernation (long, seasonal periods of deeper hypothermia, such as is seen in bears).

If similar groups of QRFP-expressing neurons are found in humans, they could represent a way to induce therapeutic hypothermia — for example, after heart attack or stroke, slowing down metabolic processes to help limit tissue damage. By contrast, during inflammatory illness, inhibition of QRFP glutamatergic neurons by the EP3 receptor might play a key part in producing fever[6]. Learning how to control these QRFP neurons could provide insight that will aid the development of new fever-reducing drugs.

The enormous range of body temperatures regulated by the QRFP neurons suggests that they and the other subpopulations of thermoregulatory neurons in the median preoptic nucleus might be the centrepiece of the brain's thermoregulatory system. But if these neurons are excitatory, and if they act on neurons that cause heat generation and conservation, then there must be an inhibitory link, almost certainly consisting of local inhibitory neurons called interneurons (Fig. 1b). This model calls for reconsideration of much of what we thought we knew about thermoregulation, in particular the physiological roles of genetically distinct subpopulations of median preoptic thermoregulatory neurons.

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Condensed-matter physics

Atomic forces mapped out by lasers

Michael A. Sentef

The forces between electrons and nuclei in solids are difficult to image directly. A study shows that these forces can instead be indirectly imaged using the light emitted when the electrons are subjected to a strong laser field. **See p.55**

One of the central goals of physics is to gain a detailed understanding of nature's building blocks and the mutual forces between them. In materials, such building blocks are atomic nuclei and the electrons that zip around between these nuclei, with forces acting on atomic length scales. Direct imaging of such forces using light is notoriously difficult and typically requires X-ray wavelengths. However, on page 55, Lakhotia *et al.*[1] demonstrate that indirect imaging is possible using visible light, even though the wavelengths of this light are about 10,000 times larger than atomic scales.

The authors achieved this feat using a method called high-harmonic generation, in which a strong laser field provides the electrons with more energy than they need to overcome the forces pulling them back to the nuclei. The shaken electrons then emit light at multiples of the laser frequency, known as high harmonics. This emission is a consequence of the nonlinearity of the energy 'landscape' that the electrons are subjected to inside the periodic lattice of nuclei when they are driven by an intense laser field.

To understand this effect, consider playing a note on a trumpet. When the instrument is played at normal strength, a pure tone is heard at the intended frequency. However, when one blows the trumpet strongly, higher overtones emerge because the amplitude of the instrument's excitation is sufficiently large to probe a nonlinear regime.

Electrons in solids are quantum-mechanical objects described by a wavefunction that determines the probability of finding them at a specific position and with a particular velocity or momentum. For free particles, momentum is the product of mass and velocity. However, electrons in solids are not free, but are affected by the potential energy provided by the uniform atomic lattice. The electrical forces applied to the electrons by the nuclei are given by the slope of the potential-energy landscape at each position (Fig. 1a) and are analogous to the gravitational forces pulling back a hiker in the mountains. But how can these forces be mapped out by shaking the electrons with a laser?

The answer to this question is best understood by considering how an electron's energy depends on its momentum (Fig. 1b). The kinetic energy of a free electron grows quadratically with its velocity or momentum,

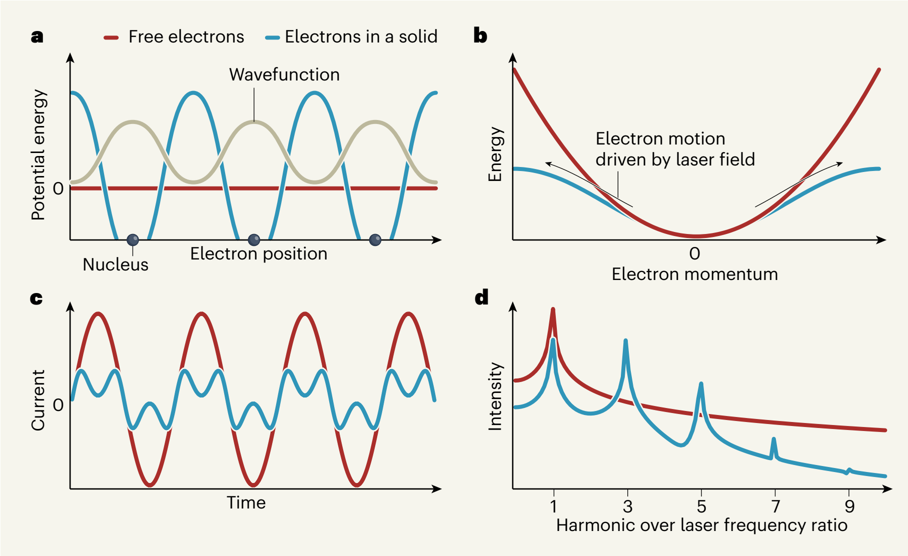

Figure 1 | High-harmonic generation. **a**, The potential energy of free electrons is zero, but that of electrons in a solid varies because these particles are attracted to nuclei located at the potential-energy minima. The wavefunction of such electrons has a periodicity determined by the positions of the nuclei. **b**, The energy–momentum relation for free electrons has the shape of a parabola. However, for electrons in a solid, the potential-energy 'landscape' changes this parabola into a shape that can be described as an energy band. When a strong laser field is applied to these band electrons, they are driven into the region of non-parabolicity. **c**, In such a field, the current of free electrons has sinusoidal oscillations, whereas that of band electrons shows deviations from these oscillations. **d**, The free electrons produce light at the laser frequency (the single peak present). Lakhotia *et al.*[1] show that the band electrons also emit light at odd multiples (high harmonics) of this frequency.

resulting in a curve known as a parabola. For an electron in a solid, the potential-energy landscape changes this parabola into an energy band that resembles the parabola at small momenta but flattens out when the electronic wavefunction reaches a momentum comparable to the inverse of the interatomic distance in the lattice. Such flattening of the energy–momentum curve corresponds to the nonlinearity that makes a trumpet play overtones.

To reach this nonlinear regime, one needs to apply a strong laser field that accelerates the electrons to large-enough momenta. Within the parabolic part of the energy band, the magnitude of the current produced by the electrons follows sinusoidal oscillations in the amplitude of the applied laser field in lockstep (Fig. 1c). However, once the nonlinearity is reached, the current deviates from sinusoidal behaviour and overtones start to emerge.

A simple way to see the connection between the non-parabolic part of the energy band and the emergence of overtones in the current is by noting that the velocity of the electrons is given by the slope of the energy–momentum curve. When the electrons are accelerated to high momenta, the band flattens out, the velocity decreases and the magnitude of the current is reduced. Because the band flattening is directly linked to the potential energy caused by forces between electrons and nuclei, the deviations from a sinusoidal current encode information about the energy landscape itself.

Lakhotia and colleagues' main achievement is the precise measurement of these deviations and the reconstruction of the underlying potential-energy landscapes inside the materials they considered. In practice, they did not record the electronic currents directly; rather, they measured the spectra of light emitted by the moving charges (Fig. 1d). These spectra contain a single peak at the laser frequency and additional peaks at odd high harmonics. The authors analysed in detail the heights of these peaks and the phases of the emitted light — the phase of a light wave specifies in which stage of an oscillation cycle the electric field of the wave is.

"The shaken electrons then emit light at multiples of the laser frequency, known as high harmonics."

To reconstruct the energy landscapes, Lakhotia *et al.* needed to assume that the atomic forces were weak compared with the driving force provided by the laser field[2]. This assumption seems to be fulfilled for the materials considered, partly because the atomic forces are not too strong. As a result, the deviation between the free-electron parabola and the flattened band is relatively small. An intriguing open question is whether a method known as high-harmonic spectroscopy[3] can be generalized to reveal detailed information about the forces inside solids when these forces are strong.

The authors also needed to assume the validity of the independent-electron picture, in which the mutual repulsion between electrons can be neglected. This picture is inappropriate for some materials more exotic than those studied here. For instance, in strongly correlated electronic materials, electron–electron interactions can lead to astonishing effects ranging from high-temperature superconductivity to Mott insulation[4] — the electronic version of a traffic jam. An ongoing research problem is to determine how these strong interactions and their weakening through laser driving[5] modify high-harmonic spectra[6,7]. Lakhotia and colleagues' paper could be seen as motivation to search for a path towards imaging such strong electron–electron interactions.

Finally, a key direction for future work concerns the dynamic imaging of the interplay between driven electrons and other excitations in strongly driven quantum materials, in particular at even longer laser wavelengths than those used in this study. The first step towards this goal is the reconstruction of interatomic potential-energy landscapes from highly displaced nuclei[8]. It will be intriguing to see how the combination of different time-domain techniques will provide a glimpse into the complex interplay of the many constituents from which fascinating material properties emerge in and out of equilibrium[9].

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