leaky BBB and cognitive impairment. sPDGFRβ elevation was independent of Aβ and tau.

The authors then looked for insight into the mechanisms by which pericytes might become injured. They focused on cyclophilin A (CypA) and matrix metalloproteinase-9 (MMP9), two proteins that are part of an inflammatory pathway implicated in *APOE4*-driven pericyte damage and BBB breakdown[6]. Levels of CypA and MMP9 in the cerebrospinal fluid were higher in *APOE4* carriers who had mild cognitive impairment than in cognitively healthy *APOE4* carriers or *APOE3* carriers who had comparable cognitive dysfunction. Again, this change was not related to increases in Aβ or tau.

Finally, the researchers generated pericytes *in vitro* from human induced pluripotent stem cells that expressed *APOE3* or *APOE4*. They found that *APOE4*-expressing pericytes secreted substantially more CypA and MMP9 than did *APOE3* pericytes. ApoE4 (but not ApoE3) secreted by pericytes activates the CypA–MMP9 pathway on nearby pericytes – the cells therefore cause their own demise. ApoE4 could also activate the CypA–MMP9 pathway in endothelial cells, which are susceptible to the harmful effects of *APOE4* (ref. 7). Therefore, injury to pericytes and endothelial cells might both cause BBB leakage (Fig. 1).

These observations cast new light on *APOE4* that runs contrary to the widely held idea that this gene variant contributes to Alzheimer's disease solely by promoting Aβ and tau accumulation[4]. Instead, it seems that BBB dysfunction might explain why *APOE4* carriers are susceptible to Alzheimer's disease. The authors' findings might also explain why *APOE4* carriers have worse outcomes following stroke or traumatic brain injury[8] than do people who carry other *APOE* variants. However, as Alzheimer's disease progresses, *APOE4* could also slow Aβ and tau clearance, exacerbating declines in cognition.

Even more striking is the finding that early drivers of cognitive impairment differ between *APOE4* and *APOE3* carriers. Montagne and colleagues' findings indicate that activation of the CypA pathway and pericyte damage might not be involved in cognitive impairment in people who carry the most common *APOE* variant, *APOE3*. But whether a leaky BBB caused by factors that are independent of pericytes (for example, damage to endothelial cells caused by Aβ; ref. 1) contributes to cognitive impairment in *APOE3* carriers remains unclear. The role of the BBB in *APOE2* carriers, which was not assessed in the current study, also remains unknown. Although *APOE2* is associated with a reduced risk of Alzheimer's disease compared with other *APOE* variants, this is unlikely to result from a more resilient BBB, because *APOE2* carriers have an increased risk of microhaemorrhages, suggesting vascular frailty[4].

Whether and how BBB breakdown leads to cognitive impairment also remains to be determined. Is it a cause or a consequence of the disease process? Evidence from mice indicates that some proteins in the blood, such as fibrinogen, damage the synaptic connections between neurons[9]. But a pathogenic role for these proteins in the human brain has not yet been demonstrated.

Irrespective of these questions, Montagne *et al.* have broadened our understanding of how *APOE4* promotes cognitive impairment. They have also demonstrated that different *APOE* statuses can promote disease through different mechanisms. A deeper appreciation of how gene variants shape Alzheimer's disease might prove crucial for more-personalized approaches to treating this prevalent and incurable disease.

Makoto Ishii and **Costantino Iadecola** are at the Feil Family Brain and Mind Research Institute, Weill Cornell Medicine, New York, New York 10065, USA.
e-mail: coi2001@med.cornell.edu

1. Cortes-Canteli, M. & Iadecola, C. *J. Am. Coll. Cardiol.* **75**, 942–951 (2020).
2. Nation, D. A. *et al. Nature Med.* **25**, 270–276 (2019).
3. Montagne, A. *et al. Nature* **581**, 71–76 (2020).
4. Yamazaki, Y., Zhao, N., Caulfield, T. R., Liu, C.-C. & Bu, G. *Nature Rev. Neurol.* **15**, 501–518 (2019).
5. Profaci, C. P., Munji, R. N., Pulido, R. S. & Daneman, R. *J. Exp. Med.* **217**, e20190062 (2020).
6. Bell, R. D. *et al. Nature* **485**, 512–516 (2012).
7. Koizumi, K. *et al. Nature Commun.* **9**, 3816 (2018).
8. Mahley, R. W., Weisgraber, K. H. & Huang, Y. *Proc. Natl Acad. Sci. USA* **103**, 5644–5651 (2006).
9. Merlini, M. *et al. Neuron* **101**, 1099–1108 (2019).

Atomic physics

Exotic helium atom lit up

Niels Madsen

An elusive type of atom known as pionic helium has been directly excited by laser light for the first time. The work establishes a promising experimental platform for probing fundamental physics. **See p.37**

Exotic atoms are those in which one or more of the constituents of normal atoms have been replaced by an exotic particle, such as an antimatter particle. These atoms can then be probed to search for any tiny discrepancies in their properties from those predicted by models using techniques that underpin the world's most accurate timekeepers, atomic clocks – and thereby opening a window on the foundations of physics. On page 37, Hori *et al.*[1] are the first to report laser excitation of helium atoms in which one electron has been replaced by a subatomic particle called a pion.

The interest in exotic atoms arises from the fact that they often facilitate the most basic experimental strategy used in physics: changing a single parameter or component in an otherwise complex system, to observe the effect. In practice, this is not as simple as it might seem. Different particles can have different masses or charges, and might interact with their surroundings differently in other subtle ways. However, such subtleties often add to the value of exotic atoms.

As the techniques needed to study exotic atoms improve, increasing numbers of scientists are working with these atoms to investigate the fundamental properties of nature. A good example of this is the 'proton radius puzzle', which arose from a study of muonic hydrogen[2] – a hydrogen atom in which the electron has been replaced by a subatomic muon particle (muons have similar properties to electrons, but have about 200 times greater mass).

Muonic hydrogen was used to determine a key property of the proton known as the charge radius, but the value obtained was about seven standard deviations away from the expected value at the time. The value obtained using muonic hydrogen has since been independently confirmed in a study of ordinary hydrogen[3], and also in experiments in which electrons are scattered from protons[4], potentially clarifying the true value of the proton radius and thus solving the puzzle. Nevertheless, muonic hydrogen aptly illustrates how exotic, sometimes short-lived, atomic systems can be used to poke holes in seemingly well-established results.

An important feature of exotic atoms that adds to their utility as probes for fundamental physics is that they are bound systems (energy is needed to pull their components apart), with multiple internal energy states. Transitions between these states are therefore amenable to study by laser spectroscopy, the most precise measurement tool in the physics toolkit. The study of transitions in atoms – and particularly in the hydrogen atom – is an ongoing effort that has spanned more than two centuries. It inspired Niels Bohr's groundbreaking model of the atom in the early twentieth century, for example, and has driven much

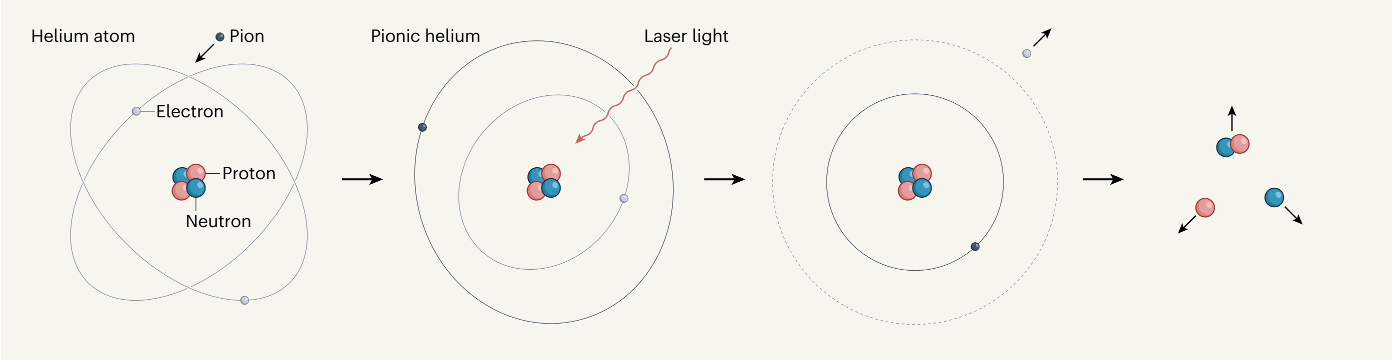

Figure 1 | How to make and excite pionic helium. Hori *et al.*[1] fired a beam of negatively charged subatomic particles, called pions, at liquid helium. When a pion struck a helium atom, it could knock out one of the electrons and replace it in a high-energy orbit around the helium nucleus (which consists of two protons and two neutrons), thus forming an exotic atom known as pionic helium. The authors fired laser light at the exotic atoms and thus observed the transition of the pion to a lower-energy orbit — a process that triggers the ejection of the remaining electron. This ejection speeds up the absorption of the pion by the nucleus (not shown), which finally breaks apart.

of the development of quantum mechanics.

Today, atomic transitions are the foundation on which all time measurements are built: a transition in the caesium-133 atom provides a reference value that underpins the International System of Units definition of the second. Therefore, spectroscopic techniques for measuring transitions are constantly being refined, and the best measurements can now reach staggering precisions — to almost 18 significant figures[5]. The most precise measurements of exotic atoms still lag some way behind, but a measurement on antihydrogen (the bound state of an antiproton and an antielectron) achieved a milestone precision of almost 12 significant figures[6], thus paving the way for extremely sensitive tests of the fundamental properties of antimatter.

In their seminal work, Hori *et al.* record the first observation of a transition in a 'pionic' helium atom. In such an atom, one of the two electrons of a helium atom has been replaced by a subatomic particle called a pion. Pions were discovered[7] by Cecil Powell and co-workers in 1947, but their existence was first predicted[8] in 1935 by Hideki Yukawa. They belong to the family of subatomic particles known as mesons, which are made up of a quark and an antiquark; quarks are the particles that make up protons and neutrons.

Pions are short-lived particles that come in positively charged, negatively charged and neutral varieties. The negatively charged pions used by Hori *et al.* have a lifetime of only 26 nanoseconds when isolated. It is thus no small feat that the experimenters not only succeeded in replacing an electron in helium atoms with a pion, but also observed the resulting exotic atom undergo a quantum transition. A further difficulty is that the lifetime of the pion in the exotic atom can be reduced to picoseconds because of its vicinity to the atom's nucleus.

The authors prepared pionic helium atoms by firing a beam of pions at a liquid-helium target. In Hori and colleagues' experiment, the helium target was cooled to a cryogenic temperature of about 2 kelvin. This allowed some pions to be captured in a weakly bound state of pionic helium, in which the pion was sufficiently far from the nucleus to be shielded from it by the remaining electron (Fig. 1). The resulting exotic atom therefore retained a lifetime of nanoseconds, which is long enough for a laser pulse to excite the nascent exotic atom.

Using a short pulse (0.8 nanoseconds) of infrared laser light, Hori and colleagues provoked a transition of the pion. This resulted in the ejection of the remaining electron, leaving a short-lived system consisting of just a pion bound to a helium nucleus. The pion was then absorbed by the nucleus, leading to the latter's break-up (fission).

> **"The authors prepared pionic helium atoms by firing a beam of pion particles at a liquid-helium target."**

The pion transition was detected by carefully removing large 'background' signals from the experimental data; this background was associated with fission products from short-lived states of pionic helium, or was generated by the pion beam itself. That left a signal from just three transitioning pionic helium atoms per hour, or an estimated three per billion exotic atoms produced. Despite the challengingly low numbers, the laser-induced signal for the transition was clearly detected, and the laser frequency at which it occurred (and which corresponds to the energy change of the transition) could be determined with an absolute precision of about five significant figures.

This result builds on Hori and colleagues' extensive experience of studying another exotic helium-type atom, in which one electron was replaced by an antiproton[9]. That work resulted in, among other things, the most precise determination so far of the ratio of the mass of the antiproton to that of the electron. However, the authors had to overcome further challenges to study pionic helium.

For example, the lifetimes of pionic helium atoms are shorter than those of antiprotonic helium and the widths of lines in its spectrum are broadened, because the excited exotic atoms undergo many collisions in the relatively dense liquid-helium target. It might be possible to reduce the density of the liquid helium to resolve these somewhat incalculable effects, although this would also lower the signal rate. It remains to be seen whether extrapolation to zero density, where collisional effects are minimized, is practicable.

Nevertheless, Hori and colleagues' work opens up a whole new experimental system for further exploration. If the above challenges can be overcome, such exploration might enable the accuracy of the mass of the negative pion to be improved by a factor of 10–100, for instance; currently, this mass is known to only six decimal places. The experiment thus paves the way to fresh insights into the fundamental constituents of nature.

Niels Madsen is in the Department of Physics, Swansea University, Swansea SA2 8PP, UK.
e-mail: n.madsen@swansea.ac.uk

1. Hori, M., Aghai-Khozani, H., Sótér, A., Dax, A. & Barna, D. *Nature* **581**, 37–41 (2020).
2. Pohl, R. *et al. Nature* **466**, 213–216 (2010).
3. Bezginov, N. *et al. Science* **365**, 1007–1012 (2019).
4. Xiong, W. *et al. Nature* **575**, 147–150 (2019).
5. McGrew, W. F. *et al. Nature* **564**, 87–90 (2018).
6. Ahmadi, M. *et al. Nature* **557**, 71–75 (2018).
7. Lattes, C. M. G., Muirhead, H., Occhialini, G. P. S. & Powell, C. F. *Nature* **159**, 694–697 (1947).
8. Yukawa, H. *Proc. Phys. Math. Soc. Japan* **17**, 48–57 (1935).
9. Hori, M. *et al. Science* **354**, 610–614 (2016).