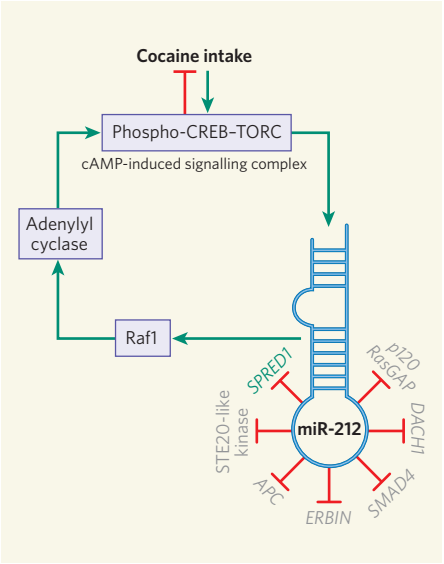


Figure 1 | Counteracting cocaine intake. Hollander *et al.*[1] find that extended access to cocaine induces expression of miR-212. This leads to decreased transcription of the genes encoding several proteins that normally repress the activity of Raf1. One such protein is SPRED1, and reduced expression of this protein, and therefore increased Raf1 activity, turns on the production of cyclic AMP (cAMP) by adenylyl cyclase. This, in turn, leads to phosphorylation and so activation of the CREB–TORC complex, which limits cocaine intake. (Figure adapted from ref. 1.)

changes occur nonetheless, leading to much greater craving and drug seeking.

Hollander *et al.* find that cocaine-seeking behaviour in rats is modulated by a microRNA called miR-212, which decreases the activity of a group of genes. They show that artificially increasing miR-212 expression leads to decreased cocaine intake under conditions of extended access, whereas blocking the expression of this small regulatory RNA increases cocaine intake.

MicroRNAs were first identified in the nematode *Caenorhabditis elegans* and were shown to silence genes involved in development[4,5]. The human genome encodes more than 1,000 possible microRNAs[6], raising the exciting possibility that these non-coding sequences could have a role in coordinating molecular changes that lead to altered behaviour, as is the case in rats. The idea presented by Hollander *et al.*[1] — that microRNAs can limit the behavioural consequences of extended access to cocaine — offers a new way of exploring the evolutionary mechanisms that protect humans against drug addiction.

An intriguing finding of this paper[1] is that miR-212 regulates the activity of the transcription factor CREB, which has been implicated in limiting the rewarding properties of cocaine. Previous studies[7,8] showed that decreasing CREB activity in the ventral striatum, an area of the brain that mediates the rewarding effects of cocaine, increased 'cocaine reward' (and vice versa). Hollander and colleagues' work suggests that extended access to cocaine in rats — a model that mimics the binge use of cocaine by human addicts — activates both CREB and one of its crucial cofactors, TORC, which together regulate the transcription of miR-212. This initiates a positive-feedback loop, further stimulating CREB–TORC activity and thereby limiting cocaine intake, but only under the extended-access conditions.

The authors go on to identify the molecular pathway by which miR-212 limits the transition to an uncontrolled intake of cocaine (Fig. 1). Most microRNAs function by blocking transcription of their target genes. Consistent with this, Hollander *et al.* show that induction of miR-212 expression leads to the decreased expression of several proteins that normally limit the activity of the small GTPase Raf1 — a key protein in the generation of the second messenger cyclic AMP by the enzyme adenylyl cyclase.

The authors identify a specific binding site for miR-212 in the promoter region of the gene encoding SPRED1, one of the proteins that limit Raf1-mediated signalling. Expression of an 'miR-212-resistant' version of the gene encoding SPRED1 blocks the ability of miR-212 to limit cocaine intake. And, when miR-212 decreases the transcription of the gene encoding SPRED1, and those encoding other Raf1 inhibitors, Raf1 activity increases, leading to greater production of cAMP and, ultimately, to increased phosphorylation and therefore activity of CREB. At each step of the pathway, the authors demonstrate that mimicking the effect of miR-212 overexpression can limit cocaine intake, whereas opposing its effect on the activity of TORC, SPRED1 or Raf1 increases cocaine intake in the extended-access model.

What are the implications of this study? Given that environmental factors can induce the expression of specific microRNAs, leading to homeostatic plasticity, it might be possible to develop treatments for drug addiction or other disorders by replicating the actions of a microRNA. The flip side of homeostatic plasticity is the induction of tolerance. It will be intriguing to investigate whether miR-212 contributes to tolerance to cocaine and whether, when extended access to cocaine is terminated, such tolerance can lead to increased withdrawal symptoms, through the unmasking of molecular alterations. ■

Marina R. Picciotto is in the Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut 06508, USA.
e-mail: marina.picciotto@yale.edu

1. Hollander, J. A. *et al. Nature* **466,** 197–202 (2010).
2. Nestler, E. J. *Neuropharmacology* **47** (suppl.), 24–32 (2004).
3. Turrigiano, G. G. *Trends Neurosci.* **22,** 221–227 (1999).
4. Lee, R. C., Feinbaum, R. L. & Ambros, V. *Cell* **75,** 843–854 (1993).
5. Reinhart, B. J. *et al. Nature* **403,** 901–906 (2000).
6. Bentwich, I. *et al. Nature Genet.* **37,** 766–770 (2005).
7. Carlezon, W. A. *et al. Science* **282,** 2272–2275 (1998).
8. Dong, Y. *et al. Nature Neurosci.* **9,** 475–477 (2006).

QUANTUM ELECTRODYNAMICS

A chink in the armour?

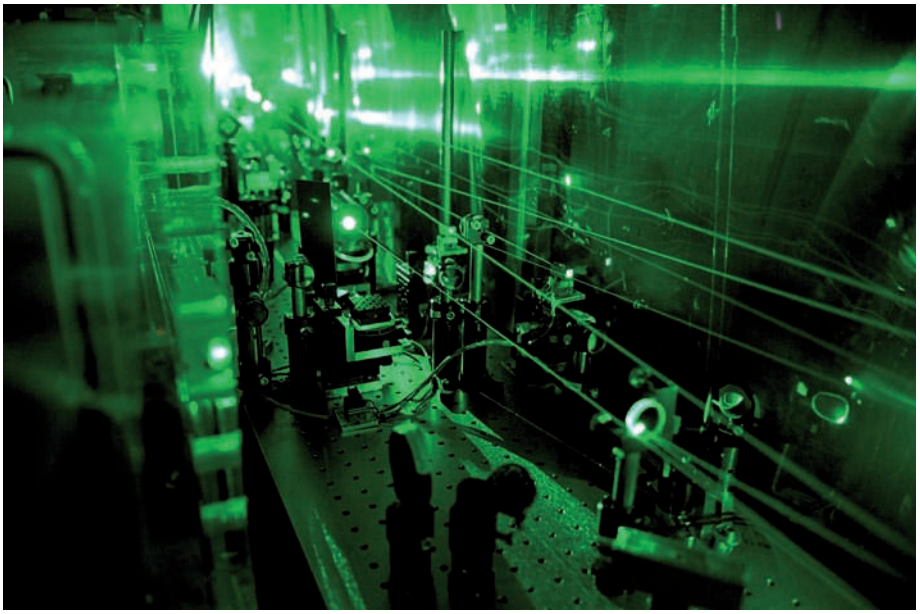
Jeff Flowers

A measurement of the size of the proton, obtained using spectroscopy of an exotic atomic system, yields a result of unprecedented accuracy — but in disagreement with values obtained by previous methods.

Richard Feynman quipped: "There's a reason physicists are so successful with what they do, and that is they study the hydrogen atom and the helium ion and then they stop." On page 213 of this issue, Pohl and colleagues[1] revisit the hydrogen atom — or, more precisely, an exotic form of it — and come up with a surprise. They describe a measurement of the size of the proton that provides a rigorous test of quantum electrodynamics (QED), the quantum theory of how light and matter interact. QED boasts the most numerically accurate predictions of any physical theory, but is based on techniques that are still unproven more than 60 years since its foundation. The authors' measurement uses a novel method that is more sensitive than any of the earlier methods. But it gives a result that is significantly discrepant from that obtained by the next most accurate method, throwing doubt on the QED calculations that underlie both methods.

Much of quantum theory was developed as a result of attempts to explain the spectral lines of the elements, in particular atomic hydrogen[2] — the bound state of a proton and an electron. Being a simple two-body system, hydrogen has a structure that, although it took many decades of work to describe by theory, is still significantly simpler than any multi-electron atom. High-precision hydrogen spectroscopy performed by Lamb and Retherford[3] in 1947 showed that the existing theoretical description of the hydrogen atom was incomplete, and this led to the new theory of QED[4]. Among the predictions of this new theory was the existence of a small splitting between two of the atom's energy levels that were previously calculated to be the same as each other, and their energy difference measured in Lamb and Retherford's

NATURE|Vol 466|8 July 2010



F. REISER & A. ANTOGNINI, PAUL-SCHERRER-INST.

Figure 1 | Part of the laser system of the muonic-hydrogen apparatus used by Pohl and colleagues[1].

experiment is now known as the Lamb shift. QED has made predictions of remarkable precision and was the prototype of field theories that followed, but its mathematical foundation is not secure and experimental verification is still being actively pursued.

Pohl and co-workers[1] at the Paul Scherrer Institute (PSI) in Switzerland have measured the Lamb shift in muonic hydrogen. In muonic hydrogen, the electron has been replaced by a negative muon — a similar particle of the same charge but 207 times heavier and unstable. The muon's larger mass gives muonic hydrogen a smaller atomic size and allows a much larger interaction with the proton, allowing the proton structure to be probed more accurately than by using hydrogen. This experiment has long been suggested as likely to give significant improvement in measurement uncertainty, but that has not been achieved until now because of considerable experimental difficulties.

At the PSI, an intense source of muons is available. Pulses of muons are stopped in hydrogen gas and some produce muonic hydrogen, a small proportion of which is in a relatively long-lived (metastable) state — with a lifetime of around one microsecond. Within this lifetime, the muonic hydrogen is subjected to an intense laser pulse (Fig. 1), and if correctly tuned, this pulse will induce a transition to an upper state separated in energy from the initial metastable state by the Lamb shift. This transition is detected through the emission of X-ray photons as the upper state decays rapidly to the ground state. Detection in a narrow time window distinguishes these laser-induced X-rays from the background X-rays, from other unwanted states produced and from muon decays. Varying the tuning of the laser frequency over many repetitions of the muonic hydrogen and laser interaction allows highly accurate measurement of the transition energy, from which the proton size can be calculated.

Previously, measurements of proton size have been made directly by scattering electrons from protons, and indirectly by spectroscopy of atomic hydrogen. Electron-scattering results are complex to analyse and the data are inconsistent. However, the available data have been analysed by Sick[5] to give a global result. Data from hydrogen spectroscopy have been compiled and combined with the electron-scattering data in the 2006 CODATA review[6]. Pohl and colleagues' new result[1] is significantly different, by five standard deviations, from the result of a combination of these previous methods (Fig. 2).

The source of this discrepancy is currently unknown. The electron scattering is the most direct method, but the interpretation of the data is open to question. In both hydrogen and muonic hydrogen spectroscopy, long, detailed QED calculations are required to produce a proton size from the experimental data. Pohl *et al.* have detailed more than 30 terms in the derivation of the equation linking their transition-energy measurement to the proton size. In calculations of this complexity, the possibility of error always exists with a magnitude that is hard to determine. In hydrogen spectroscopy, different transitions have been measured to allow the proton size and the related Rydberg constant to be extracted. In hydrogen, unlike in the muonic hydrogen reported here, these require measurement to a small fraction of the experimental transition spectral linewidth, and so details of the transition must be modelled to a high degree of accuracy — again, a possible source of error.

The discrepancy is most likely to be resolved through future work on hydrogen, muonic hydrogen, muonic deuterium and similar 'simple atomic systems'[7] — that is, systems of two bound particles. The simplicity of these systems, and hence their accessibility to calculation, allows physics to be probed, with different systems emphasizing different aspects of the physics. The hydrogen atom is the best-known two-body system. Others under study — including muonium (a bound antimuon and an electron) and positronium (a positron and an electron) — probe the QED of systems without nuclei. The helium ion (an α-particle and an electron) and antihydrogen (an antiproton and an antielectron) offer further insight into fundamental physics.

If experimental discrepancies are confirmed rather than errors being found, high-accuracy work such as that by Pohl and colleagues, not the high-energy collisions of giant accelerators, may have seen beyond the standard model of particle physics. ■

Jeff Flowers is at the National Physical Laboratory, Teddington, Middlesex TW11 0LW, UK.
e-mail: jeff.flowers@npl.co.uk

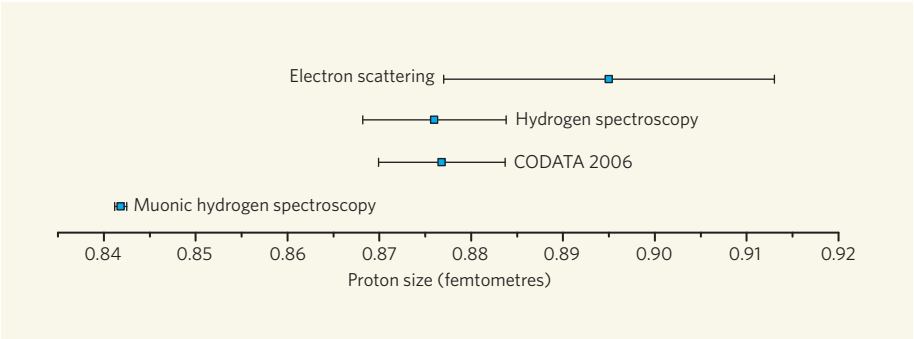


Figure 2 | Size of the proton. A comparison of the results of different methods used to measure the proton size is shown: electron scattering[5], hydrogen spectroscopy, the combination of these (both from the CODATA 2006 review[6]), and Pohl and colleagues' new measurement[1] derived from muonic hydrogen spectroscopy. The bars indicate an uncertainty of one standard deviation. The discrepancy of about five standard deviations between the muonic hydrogen result and the CODATA result, which summarizes all previous work, is clear.

1. Pohl, R. *et al. Nature* **466,** 213–216 (2010).
2. Rigden, J. S. *Hydrogen: The Essential Element* (Harvard Univ. Press, 2002).
3. Lamb, W. E. Jr & Retherford, R. C. *Phys. Rev.* **72,** 241–243 (1947).
4. Dyson, F. J. *Phys. Rev.* **75,** 486–502 (1949).
5. Sick, I. *Phys. Lett. B* **576,** 62–67 (2003).
6. Mohr, P. J., Taylor, B. N. & Newell, D. B. *Rev. Mod. Phys.* **80,** 633–730 (2008).
7. Flowers, J. L., Margolis, H. S. & Klein, H. A. *Contemp. Phys.* **45,** 123–145 (2004).