the place fields of some place cells turn off, turn on or move to a new spatial location. These activity changes result in a unique set of place cells that are active in each environment that an animal explores; this could allow the animal to identify its current surroundings and later remember which environment it visited.

O'Keefe and Dostrovsky's original work presented data from eight place cells. Technological advances over the past 50 years have allowed researchers to record simultaneously from tens to thousands of place cells, providing insight into how many such cells can work together to support navigation and memory. For example, a population of place cells can together maintain a stable position estimate over many days, even as individual cells change their activity patterns[10]. The techniques used have also revealed a rich diversity of place-cell responses. In 1971, O'Keefe and Dostrovsky saw hints that not all place cells were responsive to an animal's spatial position, and later work has since revealed that place-cell signals can also correspond to (non-spatial) variables such as specific odours[11], auditory frequencies[12] and social partners[13]. That place-cell signals can represent not only spatial position but also other unique aspects of an experience strongly suggests that hippocampal neurons provide the basis for generating and storing memories for specific experiences.

In the past few decades, versions of place cells have been discovered in primates, mice, bats and birds[14,15], pointing to these cells as underlying an evolutionarily conserved mechanism supporting memory and navigation. Moreover, O'Keefe and Dostrovsky's discovery of place cells in the hippocampus inspired researchers to explore the surrounding brain regions. This led to the discovery of neurons in the entorhinal cortices (regions adjacent to the hippocampus) that represent the position, orientation and running speed of an animal[16], as well as the position of objects[17] and the passage of time[18]. Neuronal responses to orientations, similar to those in mice and rats, have also been found in fruit flies, suggesting that the neuronal systems underlying navigation probably have evolutionarily ancient origins[19]. Together, the hippocampus and entorhinal cortices in mammals contain the conceptual elements needed to build a cognitive map with which mammals can flexibly navigate, remember and plan their way through the world.

So far, most studies have described correlations between place-cell activity and an animal's behaviour. Now, researchers can manipulate this activity in behaving animals[20], revealing potential causal links between place-cell activity, memory and navigation. For example, artificially switching on place cells that are usually active near a water reward can evoke licking behaviour in an unrewarded location[20]. Advances in genetic, molecular and cellular tools will undoubtedly continue to take the field of memory and navigation in new directions, all originating from the discovery of the place cell.

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The authors declare no competing interests.
This article was published online on 4 November 2021.

Physiology

A mediator of metabolic signals influences puberty

Alejandro Lomniczi

Variants of the melanocortin 3 receptor are associated with delayed puberty and reduced growth, suggesting that this receptor might integrate signals of metabolic status that affect body growth and sexual maturation. **See p.436**

Body growth and the onset of puberty are regulated by neurons located in a part of the brain called the hypothalamus. In the central hypothalamus, signalling by hormones called melanocortins relays metabolic information to downstream growth and reproductive centres. However, the molecular and cellular targets of these signals have not been completely elucidated. On page 436, Lam *et al.*[1] describe previously unreported mutations in the gene encoding the human melanocortin 3 receptor (MC3R) protein that seem to disrupt the receptor's function. They found that these mutations are associated with a delay in the onset of puberty as well as with reduced childhood growth, adult height and lean body mass.

Early studies[2,3] showed that the timing of pubertal onset is related more to body weight than to chronological age. These studies suggested that the body's state of growth is reported to the hypothalamus by metabolic cues that act as a signal to initiate puberty. Indeed, we now know that the increases in the hormone leptin and in the levels of glucose and insulin that occur in response to energy excess are detected by a group of hypothalamic neurons that express the melanocortin precursor peptide, pro-opiomelanocortin (POMC). It is these POMC neurons that convey information about the body's metabolic status to other hypothalamic neurons that control growth and sexual maturation[4]. However, the cellular targets and receptors involved in the melanocortin-mediated control of pubertal timing and body growth have remained unclear.

MC3R and MC4R are the two main melanocortin receptor proteins in the brain that are activated by melanocortin peptides. Humans and mice that lack functional MC4R are obese and eat excessively[5,6], but show overall normal growth and pubertal development[7]. Therefore, Lam and colleagues proposed that, if the melanocortin system influences pubertal development, a melanocortin receptor other than MC4R is probably involved. MC3R is the only other melanocortin receptor known to be expressed in the brain, and the authors therefore screened the Avon Longitudinal Study of Parents and Children (ALSPAC) data set for variations in the gene sequence of *MC3R*. (ALSPAC comprises biological, environmental, body-growth and body-development data for multiple generations of people from birth to adulthood.)

The screen identified seven rare variants of the *MC3R* gene that are predicted to render the encoded receptor non-functional. In line with

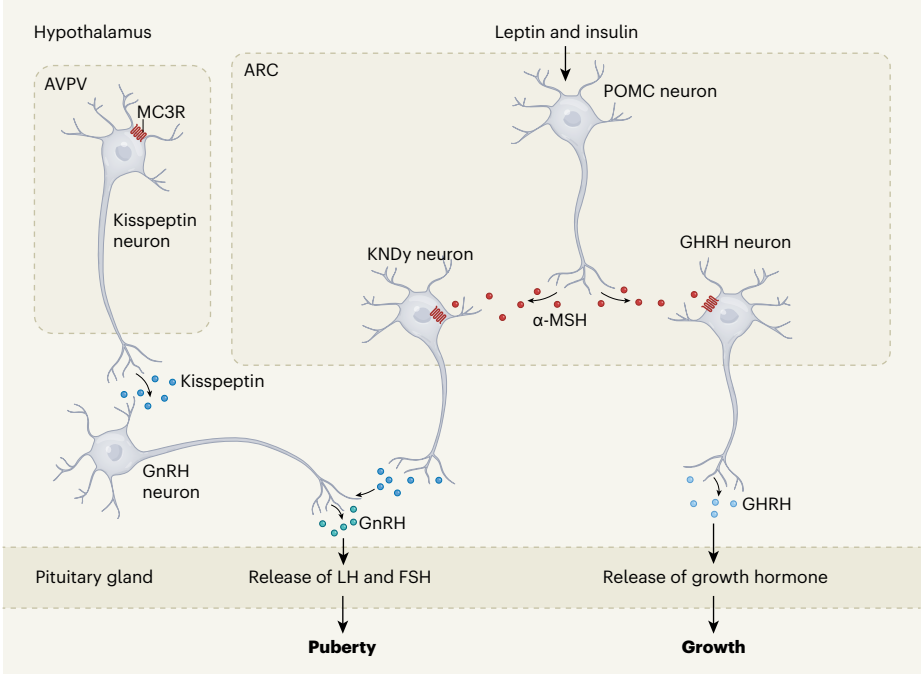

Figure 1 | A receptor implicated in the control of puberty and growth. Signals of energy status, for example the hormones insulin and leptin, promote the release of melanocortin hormones such as α-melanocyte-stimulating hormone (α-MSH) from pro-opiomelanocortin (POMC) neurons in the arcuate nucleus (ARC) of the hypothalamus, a structure at the base of the brain. Lam *et al.*[1] present evidence that melanocortins activate the melanocortin 3 receptor (MC3R) on hypothalamic neurons that regulate reproduction and growth. These include KNDy neurons, which secrete the peptide kisspeptin and thus regulate the release of gonadotropin-releasing hormone (GnRH) from GnRH neurons. GnRH controls the pulsatile release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland, influencing pubertal timing and the cyclic activity of the ovaries. Activation of MC3R on kisspeptin-expressing neurons in the anteroventral periventricular nucleus (AVPV) could affect egg-cell release in the ovaries. Activation of MC3R on neurons expressing growth-hormone-releasing hormone (GHRH) induces GHRH release, ultimately driving the release of growth hormone and body growth.

this, *in vitro* experiments revealed that three of the variants did not respond to stimulation with α-melanocyte-stimulating hormone (α-MSH), a melanocortin that normally activates MC3R. Furthermore, six individuals who carried these mutations were identified in the ALSPAC population, and – despite this small sample size – these mutations were associated with lower height during childhood and adolescence, suggesting that they affect body growth.

In an accomplished piece of work, Lam and co-workers next searched for mutations in the *MC3R* gene in data from a genome-wide association study (GWAS) of more than half a million participants in the UK Biobank, identifying three more variants of the MC3R protein. These variants were associated with the age of first menstruation in female participants and age of voice breaking in male individuals, two clinical measures of pubertal timing. Two of these rare variants, p.F45S and p.R220S, were associated with reduced growth, and p.R220S was also associated with lower than normal levels of the hormone insulin-like growth factor 1 (IGF1). Carrying a single copy of the mutated gene encoding the p.F45S variant was also associated with a 5.16-month delay in the timing of female puberty. This is the largest effect on pubertal timing associated with a single variant identified in a GWAS so far. Although these data cannot confirm a causal role for MC3R in puberty and growth, they support a potential role for this receptor in the regulation of pubertal onset, body growth and IGF1 levels. Further experiments in mice carrying these *Mc3r* variants would be needed to confirm a causal role for the receptor in growth and sexual maturation.

Mice genetically engineered to lack MC3R have more fat tissue and show reduced energy expenditure compared with wild-type mice, yet these mice have normal fertility[8]. Lam *et al.* revisited this mouse model, and found that *Mc3r*-deficient animals have slightly delayed sexual maturation compared with wild-type mice. Moreover, whereas depriving wild-type female mice of food led to their oestrous cycle (the recurring pattern of changes in activity in the ovaries) becoming longer, fasting did not affect the length of the oestrous cycle of female *Mc3r*-deficient mice. This indicates that MC3R has a role in the metabolic adaptations in oestrous cyclicity.

The hypothalamus is central to the control of sexual maturation, feeding, satiety and body growth. Neurons in the arcuate nucleus (ARC) of the hypothalamus that express the proteins kisspeptin, neurokinin B and dynorphin (called KNDy neurons) regulate the secretion of gonadotropin-releasing hormone (GnRH) from hypothalamic GnRH neurons and, therefore, control pubertal timing[9]. By contrast, neurons in the paraventricular nucleus (PVN) and ARC of the hypothalamus that produce growth-hormone-releasing hormone (GHRH) are the main regulators of body growth and development[10].

To understand the role of hypothalamic MC3R in pubertal timing and body growth, the authors analysed published databases that contain the gene-expression profiles of individual cells in the mouse hypothalamus. Out of more than 18,000 hypothalamic neurons, almost 1,200 expressed *Mc3r*, with high levels of expression in KNDy neurons as well as GHRH neurons (Fig. 1).

To confirm the specificity of this analysis, the authors used a method called single-molecule *in situ* hybridization to detect the co-expression of several messenger RNAs in individual hypothalamic neurons in slices of mouse brain. They detected *Mc3r* mRNA transcripts in KNDy neurons in the ARC, as well as in GHRH neurons in the ARC and PVN. Notably, *Mc3r* mRNA was also identified in kisspeptin-expressing neurons of the anteroventral periventricular nucleus, another region of the hypothalamus. These kisspeptin neurons are found only in female mice and control the surge of pituitary hormones that act on the ovaries to stimulate the release of egg cells. Therefore, *Mc3r* mRNA is expressed in the hypothalamic neuronal networks that control sexual maturation, the oestrous cycle and body growth. Future studies involving cell-specific deletion of the *Mc3r* gene in GHRH and KNDy neurons will be necessary to further clarify the role of MC3R signalling in pubertal development and growth.

By proposing a previously unrecognized role for the MC3R in the hypothalamus, Lam and colleagues' work takes us a step closer to understanding the central mechanisms that are involved in the global trends towards an increase in height and a decrease in age at puberty onset that have been observed over the past century[11]. These findings have potential clinical relevance. For example, the analysis of *MC3R* could be part of routine genetic analysis for individuals of disproportionately short stature who have low levels of IGF1 and delayed puberty. Moreover, the use of existing drugs that selectively activate MC3R could be explored in individuals who have delayed growth and delayed sexual maturation.

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The author declares no competing interests.
This article was published online on 3 November 2021.

Inorganic chemistry

Californium–carbon bond captured in a complex

Julie E. Niklas & Henry S. La Pierre

The scarcity and high radioactivity of the heaviest actinide elements, such as californium, make their study a formidable challenge. A landmark report describes the first structural characterization of a californium–carbon bond. **See p.421**

The detailed study of a class of organometallic compounds known as the metallocenes has driven crucial developments in areas such as catalysis, electrochemistry and nanotechnology. On page 421, Goodwin *et al.*[1] report the synthesis and characterization of a metallocene complex of californium, a member of the actinide series of elements (Fig. 1a). Substantial technical challenges had to be overcome to handle this air-sensitive complex of a highly radioactive element – just two milligrams of californium were used in the work. Remarkably, the authors report the first crystallographic measurement of a californium–carbon bond. Organometallic complexes of actinide ions have emerged as a frontier of research that challenges accepted models of bonding in coordination complexes (compounds consisting of a central atom or ion bound to ligands). Goodwin and colleagues' findings will help to map periodic trends of physico-chemical properties across the heavy actinides.

Californium (Cf) is not found in nature, and was first produced in 1950, enabling the identification of a range of its chemical and nuclear properties[2]. The advent of programmes to produce elements heavier than plutonium (the transplutonium elements) subsequently allowed larger quantities of californium to be prepared. Currently, californium is the heaviest element for which greater than microgram quantities are available, enabling measurement of its bulk properties in compounds. Nevertheless, in contrast to the rapidly developing chemistry of the naturally occurring early actinide elements thorium and uranium, the chemistry of californium (and of the other transplutonium elements) remains severely constrained by the element's high radioactivity, low abundance and high cost. The field has therefore received limited attention since the 1970s.

Goodwin *et al.* address this knowledge gap by preparing and characterizing a californium metallocene complex (Fig. 1b). They chose to use the californium-249 isotope, because it has a longer half-life (351 years)[2] than other isotopes of this element. To put the radioactivity of this isotope into perspective, its specific activity is roughly 12 million times that of depleted uranium (uranium-238, which itself requires special handling protocols).

In addition to the challenges involved in handling the isotope on the requisite small scale of available isotope, there were concerns that radiolytic decay of californium might damage the samples. The authors therefore tuned the synthesis of the metallocene so that the crystalline complex could be produced in a day. They also optimized the synthesis in model reactions using ions of the lanthanide series of elements. Lanthanides are cheaper and easier to handle than is californium, and their ions have a similar radius to the californium ion, which makes them useful substitutes in model reactions.

Goodwin and colleagues also prepared a metallocene using americium-241, an actinide that is close to californium in the periodic table, with a similar radioactive decay rate, and which emits α-particles that have similar energies to those emitted by californium-249. They used this metallocene to investigate the potential of radiolysis to affect which products formed in their reactions, and the products' crystal stability. Armed with all the information from the model studies, the authors went on to successfully isolate and characterize the target californium metallocene, which turned out to have a 'bent' structure (the two organic ligands in the complex are not parallel; Fig. 1b).

The first actinide metallocene[3] was a uranium compound isolated in 1968, and its characterization redefined our understanding of metal–ligand bonding in the actinide elements[4]. In the past few years, metallocene frameworks have also afforded the first structural characterization of actinide–carbon bonds beyond uranium in the periodic table (plutonium[5,6] and americium[7]). Goodwin and colleagues' work extends structurally characterized actinide–carbon bonds to californium, and enables the bonding and electronic

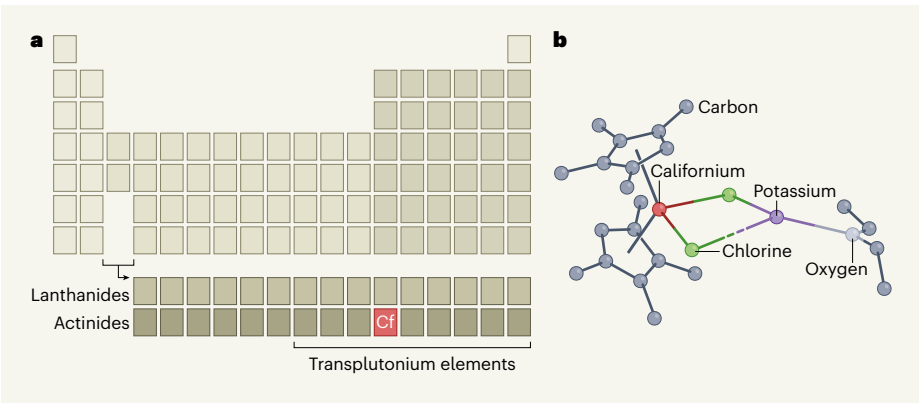

Figure 1 | An organometallic complex of californium. a, The lanthanides and actinides are two series of elements in the periodic table, and the transplutonium elements are actinides that are heavier than plutonium. The actinide californium (Cf) is highly radioactive and very scarce, and its compounds are therefore extremely difficult to prepare and analyse. **b**, Goodwin *et al.*[1] have synthesized the organocalifornium complex $[Cf(Cp^{tet})_2Cl_2K(OEt_2)]_n$ and obtained its crystal structure (shown). The complex adopts a 'bent metallocene' configuration in which the two ligands twist away from a parallel configuration to accommodate the Cf^{3+} ion as it binds to (coordinates) two chloride ions. The chloride ions are stabilized by a potassium ion (K^+), which coordinates the oxygen atom of a solvent molecule. Cp^{tet} is an organic ligand (tetramethyl-cyclopentadienyl); Et, ethyl group (C_2H_5). Hydrogen atoms are not shown.