Collectively, these data show that the durability of a drug's effect on social-reward learning can vary significantly, approximately in line with the duration of the drug's acute effects in people. This provocative piece of evidence suggests that the duration of acute effects, and not the drugs' receptor targets, might be what matters for their effect on social behaviour.

To dig into the neural mechanism underlying their observations, Nardou *et al.* focused on the hypothesis that the drugs might not change synaptic wiring directly, but instead increase the likelihood that the strength of signalling between neurons is altered if the synapses are stimulated by other neurotransmitters — a phenomenon known as metaplasticity. The social reward conditioned place preference assay has previously been shown[12] to rely on a type of metaplasticity in which signalling by the hormone oxytocin depresses activity across synapses (known as long-term depression) in a brain region called the nucleus accumbens. Nardou and colleagues recorded synaptic activity from medium spiny neurons in slices of nucleus accumbens obtained from mice treated with ketamine, MDMA, LSD or ibogaine. The drugs produced telltale signs of oxytocin-dependent metaplasticity. Importantly, LSD's metaplastic effects were longer lasting than were those of ketamine, corroborating the behavioural findings.

Finally, RNA sequencing of neurons in the nucleus accumbens revealed that the various psychedelics increase the expression of genes associated with the extracellular matrix (a network of proteins and molecules that surround and support neurons, including those at synapses). Restructuring of the matrix can permit neural plasticity[13], so the authors propose that matrix remodelling might be a key cellular process that underlies the actions of psychedelics.

Together, Nardou and colleagues' work indicates that the timing of a drug's action and the metaplasticity it induces are key elements of psychedelic-induced neural plasticity. But many aspects of the process remain to be defined. For instance, given that the drugs target distinct receptors, it is unclear how their effects can converge to induce metaplasticity in the nucleus accumbens. Despite the authors' findings, there is debate as to whether oxytocin receptors in the nucleus accumbens are needed for MDMA to mediate pro-social preference[14]. It also remains to be seen whether psychedelics' effects on non-social behaviours are linked to their pharmacokinetics, and whether metaplasticity is the mechanism that governs the action of psychedelics in other brain regions. This might be difficult to test *in vivo* because of the many neurotransmitter systems that are active concurrently in live animals.

The study has implications for the clinical use of psychedelics. An attractive feature of psychedelic-assisted therapy is the durability of the potential benefit — for instance, one or two doses of psilocybin is reported to reduce depression symptoms for months[2,3]. Nardou and colleagues' work shows that different psychedelics could yield behavioural effects that last for varying times related to the length of their acute actions. The work raises the interesting question of whether a psychedelic's subjective effects in humans are crucial for its efficacy in treating mental-health problems. If so, newly synthesized non-hallucinogenic analogues of these drugs might not yield therapeutic benefits, contrary to previous proposals[15]. However, further testing will be required to confirm this.

Clearly, not all types of neural plasticity are good for the brain — for example, plasticity caused by drugs of misuse, such as cocaine, nicotine and amphetamines, can result in addiction[16,17]. Moreover, some aspects of drug-induced plasticity observed *in vitro* might not reflect a drug's effects *in vivo* (although they might still be valuable as a measurement for drug screening). By appreciating and embracing the varieties of drug-induced plasticity, we can begin to unpack the nuanced mechanisms by which each drug acts. This, in turn, could lead to improved clinical protocols and accelerate drug discovery, to realize psychedelics' therapeutic potential.

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Evolution

The long infancy of sterol biosynthesis

Fabien Kenig

A newly discovered fossil record of steroid molecules, spanning 1.64 billion years, points to ancient organisms in the eukaryotic domain being capable of only early steps in the synthesis of sterol molecules. **See p.767**

The biosynthetic pathways that give rise to molecules called sterols are well established in the scientific literature. These pathways include the modifications (oxidation and cyclization) of a molecule called squalene to form lanosterol and cycloartenol, which are protosterols — precursors of other sterols. Numerous other steps are then needed to make cholesterol and other related sterols (known as crown sterols) that are found in organisms with cells that have a nucleus (eukaryotes); organisms called crown eukaryotes are either living eukaryotic species or extinct eukaryotic species that are descended from the last common ancestor of all living eukaryotes. Under favourable conditions, the carbon backbones of sterols can be preserved in ancient sedimentary rocks as molecular fossils, which are versions of the molecules that arise as a consequence of geological processes. Brocks *et al.*[1] report on page 767 that their exploration of molecular fossils has uncovered an approximately 640-million-year-long period of Earth's history when sterol biosynthesis had not yet evolved the complex pathways that exist today.

Brocks *et al.* show that sedimentary rocks dated to between 1,640 million years and approximately 1,000 million years ago (a time frame corresponding to the mid-Proterozoic

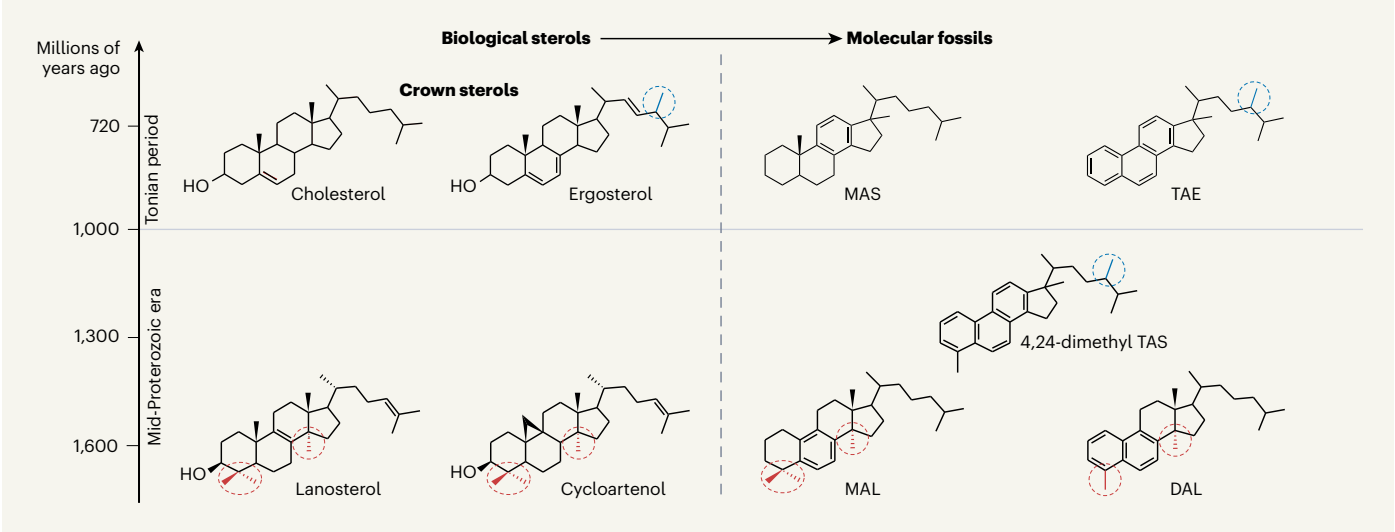

Figure 1 | Ancient sterol molecules. Sterols, termed crown sterols, such as cholesterol and ergosterol, are hallmarks of living eukaryotic species (a group that includes animals and plants). Signs of crown sterols are found in rocks from the Tonian period in the form of molecular fossils — versions of the molecules that arise as a consequence of geological processes (monoaromatic sterane (MAS) for cholesterol and triaromatic ergostane (TAE) for ergosterol). Brocks *et al.*[1] searched for clues to when crown sterols appeared, by examining ancient rocks. In rocks from the mid-Proterozoic era, the authors found molecular fossils that included monoaromatic lanosteroid (MAL) and diaromatic lanosteroid (DAL). These correspond to original molecules called protosterols (lanosterol and cycloartenol). Another molecular fossil found was 4,24-dimethyl triaromatic steroid (TAS), which corresponds to an original molecule called an ursterol (not shown). However, these protosterols and ursterols functioned as end products rather than pathway intermediates. On the evolutionary journey from sterols to crown sterols, three methyl groups (red) are removed, step by step, from the sterol, flattening one side of the molecule and boosting its function in the membrane. Methyl groups added on the side chain are shown in blue.

era), contain abundant molecules, known as aromatic steroids, that are molecular fossils of protosterols, but that these rocks show no signs of molecular fossils of crown sterols. Brocks and colleagues also clearly show that later, around 800 million years ago, during the Tonian period (which spanned 1,000 million years ago to 720 million years ago), the oldest-known molecular fossils of crown sterols (the aromatic hydrocarbons of cholesterol and ergosterol) replaced fossil protosterols as the most abundant fossil sterols.

Nearly all eukaryotes can synthesize one or several crown sterols, and it is estimated that the last eukaryote common ancestor (LECA) had the ability to synthesize them as well[2]. The absence of molecular fossils of crown sterols during the mid-Proterozoic favours the proposal that the LECA appeared later, between 1,200 million and 1,000 million years ago, rather than earlier, between 1,800 million and 1,600 million years ago[2].

Brocks and colleagues' data-gathering approach was unusual and creative because aromatic steroids were used for the first time to establish a long-term mid-Proterozoic record of fossil steroids (molecules that have sterol precursors). This method enabled the authors to obtain substantial steroid data from mid-Proterozoic sediments. Given that the LECA was thought to have appeared much earlier[2], the absence of crown steroids in these data seemed abnormal and this absence was proposed to be the result of preservation bias (a change in the factors that affect the potential of these molecules to become molecular fossils). The identification of these aromatic compounds enabled the authors to connect these molecular fossils to their original biological precursors, and reveal the fascinating fact that they derive only from protosterols.

The presence of the molecular fossils of protosterols reflects the existence of a mid-Proterozoic protosterol-using group of organisms (Fig. 1). This biota was using these protosterols as end products. These compounds were not yet the short-lived intermediates used in the biosynthesis of more-refined crown sterols, as is the case for nearly all eukaryotes. Konrad Bloch, who won a Nobel prize in 1964, in part for his work on sterol biosynthesis, predicted such a possibility when he became interested in why sterols evolved[3].

"The authors searched for clues to when crown sterols appeared, by examining ancient rocks."

In an essay[4] entitled 'Evolutionary perfection of a small molecule', Bloch discusses molecules called ursterols, intermediate molecules in the synthesis of crown sterols. He suggests that there were previous organisms in which ursterols were useful end products that had the same role as crown sterols in controlling the fluidity of cellular membranes. It is notable that Brocks *et al.* show the presence of a type of molecule (an ursterol-derived steroid termed 4,24-dimethyl triaromatic steroid) in approximately 1,300-million-year-old sedimentary rocks, indicating that sterol biosynthesis at that time had already evolved to produce ursterols from protosterols. Another 500 million years separate this molecular fossil of an ursterol from the first occurrence of molecular fossils derived unambiguously from crown sterols.

What organisms are responsible for these ancient protosteroids and ursteroids? The enzymes squalene monooxygenase and oxidosqualene cyclase, which enable the oxidation and cyclization of squalene, respectively, are necessary for the synthesis of protosterols, are ubiquitous among living eukaryotes and were present in the LECA[2]. These enzymes are not present in another branch of life, archaea, and no archaeal microorganisms synthesize sterols.

By contrast, genes encoding these enzymes have been identified in some bacteria, notably those in the bacterial groupings Myxococcales and Methylococcales. The latter groupings have been considered to have ancient origins on the basis of evidence from phylogenetic trees involving the genes that encode squalene monooxygenase and oxidosqualene cyclase[5,6]. These two groups of present-day bacteria produce molecules of cholesteroids and ursteroids that could result in molecular fossils; however, these were not detected in sediments older than 800 million years old. Therefore, it seems unlikely that Myxococcales and Methylococcales contributed to the ancient protosteroids detected. Another argument

weakening the proposal of a bacterial origin for these protosteroids is the occurrence of 4,24-dimethyl triaromatic steroid around 1,300 million years ago, the potential precursors of which have not been observed in bacterial extracts.

Yet, as Brocks and colleagues indicate, contributions from bacteria, living or extinct, to the steroid landscape cannot be fully ruled out. Before the time of the LECA, the ability to form protosterols was most probably also present in extinct eukaryotic relatives – such species are known as stem-group eukaryotes. This capacity to form protosterols might have been transferred from ancient bacteria to eukaryotes through a process called horizontal gene transfer[7], although some argue that this transfer occurred in the reverse direction[5,6].

For 640 million years of the mid-Proterozoic era, protosterols were the main, if not the only, steroid players. In the Tonian period, after an approximately 200-million-year-long data gap, at around 800 million years ago, the protosterol world seems to have declined, whereas crown steroids progressively took over the landscape of aromatic steroids. The Tonian is already considered a key interval of Earth's history on the basis of a molecular fossil distribution that reflects the transition from a bacterium-dominated marine ecosystem to a crown-eukaryote-rich environment that also included red algae[8]. Now, the Tonian period might be known as the time when crown eukaryotes took over marine ecosystems at the expense of protosteroid-producing stem-group eukaryotes.

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Metrology

Clocks synchronized at the quantum limit

David Gozzard

Time signals have been transmitted across 300 kilometres with an accuracy and precision limited only by the quantum nature of photons. The feat promises to revolutionize high-precision science using satellites. **See p.721**

Communications networks, satellite navigation and fundamental-physics experiments that test the general theory of relativity are just a few of the diverse systems that rely on networks of modern atomic clocks. These clocks are precise to a few parts in 10^{18}, which is roughly equivalent to being able to measure the time between now and the Big Bang with an uncertainty of only one second[1]. However, to take advantage of this precision, the time signal from the atomic clock needs to be transmitted reliably. On page 721, Caldwell *et al.*[2] demonstrate a technique that could be used to transmit atomic-clock time signals between Earth and satellites without compromising the signals' precision and accuracy, which are limited only by the quantum nature of light.

Atomic clocks keep time using the frequency of light emitted by electrons as they transition between energy states in an atom. Optical atomic clocks use intersecting laser beams to trap the atoms, and these beams are engineered so that the frequency of the laser light has very little effect on that emitted by the electrons. Time signals from optical atomic clocks need to be transmitted using lasers that send these signals through fibre-optic cables or through the air, in a process called optical

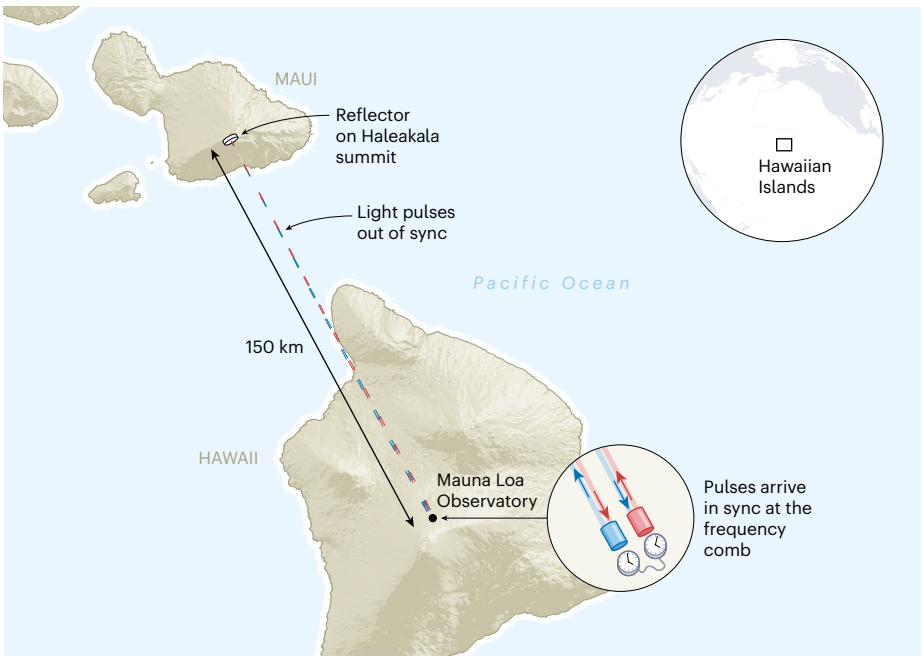

Figure 1 | Precise time synchronization between distant clocks at the quantum limit. Optical atomic clocks are high-precision timekeepers, but using them in networks (for example, those linking Earth with satellites) requires time signals to be transferred with similar precision. Caldwell *et al.*[2] paired such clocks with optical frequency combs (lasers producing precise, regular light pulses) to transmit a reflected signal between the Hawaiian volcanoes Mauna Loa and Haleakala and back – a distance of 300 kilometres. They used the arrival-time difference of pulses sent from one clock–comb pair to the other to calculate the time difference between clocks with a precision that approached the quantum limit, which is set by the number of photons transmitted. The clocks were connected so that the time transfer could be verified, and the pulse rates of the two combs were adjusted to scan possible time differences before being steered to pulse in sync.