METABOLISM

A lipid for fat disorders

A high-fat diet often leads to metabolic disorders such as diabetes, fatty liver disease and obesity. One lipid, however, might mitigate these effects through an unexpected signalling role in the nucleus. SEE LETTER P.506

HOLLY A. INGRAHAM

Lipids are best known for their integral role in biological membranes and as signalling molecules in the cytoplasm. Rarely is their importance in nuclear processes appreciated, even though it has been known for decades that lipids and the machinery that modifies them can be found in the nucleus[1]. On page 506 of this issue, Lee and colleagues[2] explore the nuclear activities of lipids, showing that a particular species of the phospholipid phosphatidylcholine (which is a component of the food supplement lecithin) controls transcriptional programs. Their data also suggest that targeting lipid signalling in the nucleus might be of value for treating human metabolic diseases.

Structural studies[3,4] have shown that phospholipids bind to the NR5A subclass of nuclear receptor. Building on these observations, Lee *et al.* set out to find a phospholipid ligand that activates the nuclear receptor LRH-1 (also known as NR5A2), which is important for bile-acid homeostasis[5]. They reasoned that such an agonist would increase bile-acid levels and reverse conditions associated with fatty liver disease. Non-alcoholic fatty liver disease can lead to hepatic steatosis, which is often associated with other metabolic disorders, including obesity, insulin resistance and type 2 diabetes.

After screening several different phospholipids in cell-based assays, the authors identified two short-chain phosphatidylcholine species that, at high concentrations (100 μM), strongly activate LRH-1. Of these, they focused on dilauroyl phosphatidylcholine (DLPC) — a species with two saturated 12-carbon fatty acyl chains (Fig. 1).

A previous structural study[6] showed that bound phosphatidylcholine nestles tightly into LRH-1's closest homologue, SF-1 (also known as NR5A1). It would therefore be expected that both DLPC and a longer-chain phosphatidylcholine called DPPC would also bind to LRH-1. Intriguingly, however, Lee *et al.*[2] report that DLPC, and not DPPC, increased LRH-1 activity. Consistent with this selective activation, they also found that a 1:1 molar ratio of DLPC, but not DPPC, could displace phospholipids bound to LRH-1. Moreover, when the authors administered these phosphatidylcholines to mice orally, DLPC elevated the levels of some, but not all, LRH-1 targets in the liver and increased the serum levels of bile acid.

Emboldened by these positive results, Lee and co-workers put DLPC to a final test to investigate whether this phospholipid might reverse diet-induced insulin resistance and fatty liver disease in mice. They fed the mice a high-fat diet (the equivalent of a continuous rich, greasy human diet) for nearly four months, to make them fat and diabetic. The authors then gave these metabolically challenged animals an oral dose of DLPC (100 milligrams per kilogram of body weight per day) for another three weeks.

The physiological effects of DLPC were truly impressive, reversing the metabolic problems commonly observed with a high-fat diet and obesity. Compared with control animals, glucose homeostasis and insulin signalling were substantially improved, and the histological hallmarks of fatty liver significantly diminished.

This paper[2] firmly establishes the beneficial actions of DLPC. But how does this trace component of lecithin perform its metabolic magic? The authors posit that DLPC functions as a natural ligand for LRH-1. In favour of this hypothesis, they discovered that almost all of DLPC's therapeutic benefits disappear when LRH-1 is genetically ablated in the liver. Coupled with their cellular data, this observation makes for a compelling case that DLPC is a ligand for LRH-1. But there is ample room for sceptics and alternative models, especially given the extremely high levels of DLPC that Lee and colleagues used in their cellular studies. For example, DLPC might target LRH-1 indirectly, either by triggering a signalling cascade or by serving as a metabolic precursor for the 'real' lipid ligand of LRH-1.

The work also raises other questions, beginning with the basic one of how DLPC enters the cell. Could a dedicated flippase enzyme or a transporter facilitate its entry? And once inside the cell, how does it reach the nucleus? Is it shuttled there by specialized phospholipid-transfer proteins? If DLPC does make its way into the nucleus to bind LRH-1, could existing synthetic ligands[7] mimic its cellular and physiological effects?

Equally perplexing are the selective effects of DLPC compared with DPPC, which share identical head groups and differ only in their acyl-chain length (12 and 16 carbons, respectively; Fig. 1). How does this difference affect these phospholipids' binding affinities and change receptor activation? If we assume, on the basis of structural studies, that the head groups are similarly positioned at the 'mouth' of the ligand-binding pocket, what path do the buried acyl chains take to account for the vastly different activities observed for DLPC and DPPC? Such questions merely underscore both the challenge and the mystery of lipid signalling in the nucleus.

What emerges from Lee and colleagues' work[2] is that, surprisingly, phosphatidylcholines reverse some of the consequences of a high-fat diet in rodents. Consistent with this is the earlier finding[8] that 1,2-dilinoleoyl-*sn*-glycero-3-phosphocholine — the major component in soya bean lecithin — was partially effective in treating fatty liver disease (note that this phosphatidylcholine species is also abbreviated to DLPC but differs from the DLPC used in the current study[2]). And, more recently, it has also been reported[9] that injection of another phosphatidylcholine called POPC into the portal vein decreases hepatic steatosis in mice, possibly by binding and activating another nuclear receptor, PPARα. On the basis of this evidence[2,8,9], dietary phosphatidylcholines could certainly offer a new option for treating human

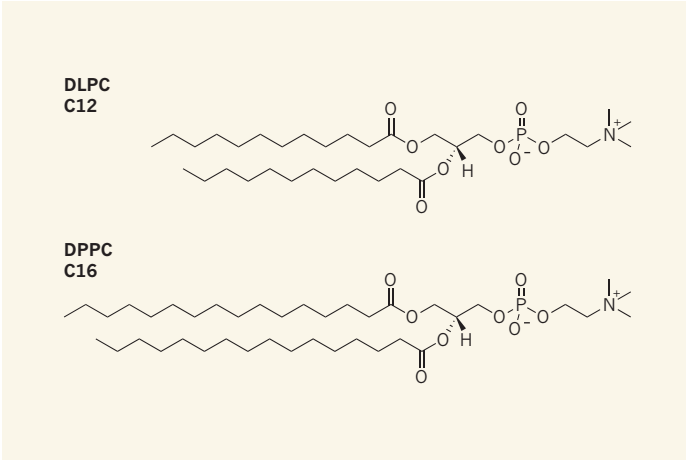

Figure 1 | Length matters. Lee *et al.*[2] investigated the effects of two phosphatidylcholine species, DLPC and DPPC, on activation of the nuclear receptor LRH-1. They found that only DLPC could activate LRH-1 and lead to improved glucose homeostasis in fat, diabetic mice. The two phospholipids differ only in the length of their fatty acyl chains (12 compared with 16 carbons), which could account for their different binding affinities to LRH-1.

metabolic disorders. But regardless of whether phospholipids can mitigate decades of bad eating habits, this study illustrates a potentially powerful role for phospholipid signalling in the nucleus. ■

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50 Years Ago

The Borneo earless monitor lizard (which forms, with two American lizards, the family Helodermatidae) is known from less than ten specimens … A live specimen measuring 13 in. (about average size to date) was obtained only a mile from our own archaeological base camp … In most of its behaviour it resembled a nocturnal snake. Though taken from a hole in the ground, the front legs are so weak that it is difficult to conceive of its burrowing with these. The strong snout and head were used to enlarge any ground weakness, however … It showed no inclination to bite either the handler or anything else (including food). It seems unlikely, therefore, that it is poisonous as has often been suggested.
From *Nature* 24 June 1961

100 Years Ago

Britain's Birds and their Nests — Another gorgeous volume on Britain's birds and their nests! … Happy the publishers, and authors we presume, supported by a public with so insatiable an appetite for British ornithology … We must, however, confess to considerable disappointment in the volume before us. The text is excellent. Indeed, the various biographies are pleasantly written … But it is with the plates that fault is chiefly to be found. They are all "very pretty," but we have more of art than of nature in them. Without exception the species … depicted are the most "proper" series of British birds we have ever made the acquaintance of. They never foul the ground, when 'tis their nature to; they never disturb a blade of grass or a single petal of the beautiful flowers that emborder their nests in nearly every case. They are indeed the most aesthetic company we have yet met with, in the choice of nesting sites.
From *Nature* 22 June 1911

QUANTUM PHYSICS

Correlations without parts

Quantum correlations between the parts of composite systems have long fascinated physicists. There is now compelling evidence that such correlations can also occur in systems in which no parts can be identified. SEE LETTER P.490

ADÁN CABELLO

Quantum mechanics is arguably the most accurate and successful theory in the history of science. But unlike the case for special relativity, for which two physical principles suffice to derive the whole theory, physicists are still seeking the entire set of underlying principles for quantum mechanics. Recently[1,2], they have been trying to understand one of the most intriguing predictions of quantum mechanics: that quantum correlations violate mathematical relationships known as Bell inequalities, which are valid for any local realistic (classical) theory, but that they do so only up to a certain value, whereas more general theories allow violations up to greater values. On page 490 of this issue, Lapkiewicz *et al.*[3] describe an experiment suggesting that a wider perspective, beyond Bell inequalities, is needed to understand why quantum correlations can attain only certain values.

In Bell-inequality experiments (Fig. 1a), tests are performed on two widely separated parts of a composite system. The experimenters then extract the correlations between the outcomes of each of several pairs of tests. In any theory in which the outcomes of these tests are pre-established, the sum of these correlations cannot take a value beyond a certain upper limit. However, quantum mechanics predicts greater values.

In Bell-inequality experiments, the physical separation between the tests has a crucial role: if it is large enough, then the decision of what test is performed in one location cannot influence the outcome of the test performed in the other location, unless there is an instantaneous influence of the two tests on each other. If the outcomes were pre-established, then instantaneous influences would be required to explain quantum correlations. But this is too high a price to pay, because it is impossible to fit instantaneous influences into any theory in which such influences travel at a finite speed.

Quantum correlations have been experimentally observed in tests that are separated widely enough to prevent any influence that travels at the speed of light[4] (Fig. 1a). However, they have been found to have the same values whether the distance between the two experiments is one metre[5] or a few micrometres[6]. What's more, quantum correlations display the same values when two compatible tests are performed on a single system[7] (Fig. 1b, c). Therefore, although distance makes quantum correlations more fascinating, it apparently plays no part in the values that quantum correlations can attain.

Why should one care about quantum correlations between compatible sequential tests on the same physical system instead of about Bell experiments? There are two reasons. The first is that, to violate a Bell inequality, a particular type of quantum state is needed; these are called entangled states and cannot be prepared by local operations and classical communication. This might suggest that composite systems and entangled states are essential for quantum correlations. However, before Bell inequalities were introduced, Kochen and Specker[8] noticed that quantum mechanics is in conflict with classical physics even for non-composite systems. This conflict can be converted into experimentally testable violations of classical correlation inequalities[9] and