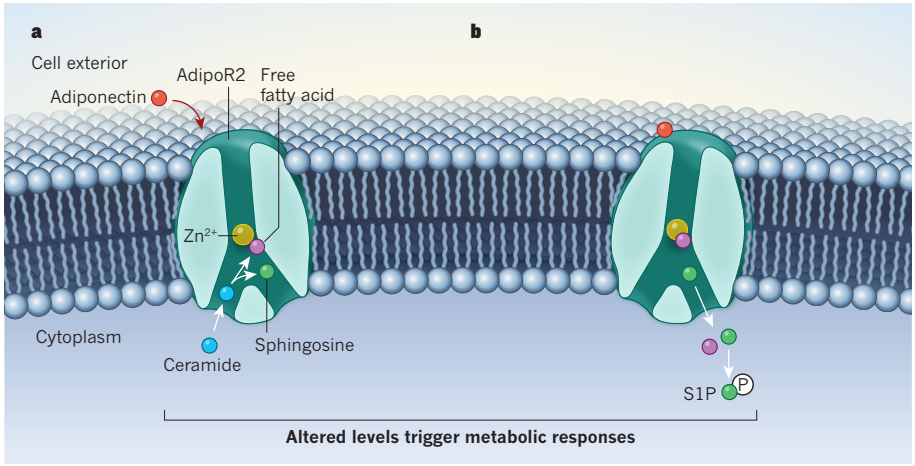

Figure 1 | Adiponectin receptor activity crystallized. Vasiliauskaité-Brooks *et al.*[5] resolved structures of the membrane-spanning adiponectin receptor 2 (AdipoR2) protein, which is activated by binding of the hormone adiponectin and mediates glucose and lipid metabolism. **a**, The structures reveal that an internal tunnel spans AdipoR2, with a zinc ion (Zn^{2+}) positioned in a binding pocket where the tunnel splits to form two entry points to the cytoplasm. On adiponectin binding, the lipid ceramide enters the tunnel and is hydrolysed to form two molecules: sphingosine and a free fatty acid bound to the Zn^{2+}. **b**, The molecules are released into the cell, where sphingosine is readily phosphorylated to sphingosine 1-phosphate (S1P). Changes in the cellular levels of ceramide, sphingosine, S1P and free fatty acids drive metabolic responses to adiponectin.

The structures, in which the hydrophobic pocket is imaged at higher resolution than in the previous AdipoR structures[14], revealed that AdipoR2 co-crystallizes with a fatty acid, which is located inside the hydrophobic binding pocket. The pocket forms part of a tunnel that spans the receptor, with one exit into the transmembrane region and two facing the cytoplasm (Fig. 1). Vasiliauskaité-Brooks *et al.* next provided evidence that AdipoR2 binds to and hydrolyses ceramide. Structural analysis, along with biochemical data and computational models, revealed the conformational changes that enable enzymatic activity: ceramide binding is followed by a rapid rearrangement of the zinc binding site, leading to ceramide cleavage to form a free fatty acid in the binding pocket and a sphingosine molecule in part of the tunnel exposed to the cytoplasm. The sphingosine may be free to drift into the cell, providing an explanation for why it is not observed in the researchers' crystal structures.

The authors also generated a structure of AdipoR1 by reanalysing previous structural data[14]. AdipoR1 did not reveal the same tightly bound fatty acid and buried catalytic cavity as AdipoR2. Instead, the catalytic site and substrate binding domain are completely accessible to the inner leaflet of the plasma membrane. Nonetheless, biochemical data confirmed that AdipoR1 has adiponectin- dependent, inherent ceramidase activity.

These observations are of great importance, because they offer highly refined structural insights into the basic functions of AdipoRs that can be combined with physiological evidence from mouse studies to provide detailed mechanistic insights into receptor function. However, major questions remain. For instance, we still do not understand the structural basis for the interaction of adiponectin with its receptors. Furthermore, although the authors' data clearly indicate that the enzymatic activity of AdipoRs is independent of other factors *in vitro*, it remains to be seen whether any accessory molecules can further enhance activity *in vivo*.

Finally, although Vasiliauskaité-Brooks and colleagues' biochemical experiments show that the presence of adiponectin increases the ceramidase activity of either AdipoR 25-fold, they cannot exclude the possibility that these receptors also possess another lipid hydrolase activity that could govern downstream signal transduction. Analyses of the lipid make-up of cells undergoing signal transduction and thorough screening of AdipoR activity in the presence of lipids other than ceramide could shed light on this issue.

Adiponectin sensitizes liver and fat cells to insulin in mice to promote nutrient uptake[4,10,15]. Moreover, circulating levels of adiponectin are higher in lean humans than in obese individuals, and correlate with fat-cell health and lowered risk of developing diabetes and heart disease. Thus, activation of signalling pathways downstream of adiponectin might help to prevent the development of insulin resistance and type 2 diabetes. The current study should greatly aid the quest to design drugs that promote AdipoR activity. Adiponectin mimetics might unleash the full antidiabetic potential of these receptors. ■

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50 Years Ago

Charles Darwin was in the habit of cutting from his notebooks those pages which were most useful to him when he was preparing to write his large book on natural selection, of which *Origin of Species* was but an abstract … Two sets of pages have since been found in the British Museum … Because the notes are concerned with transmutation of species, most of them refer to examples which illustrate some aspect of adaptive variation. Geographical distribution was very important to Darwin and he recorded examples of species which are peculiar to particular areas and of closely related species living together, such as two bears in Borneo and Sumatra which differ only in the form of a white mark on the breast.

From *Nature* 8 April 1967

100 Years Ago

In reference to the inquiry of Dr. Walter Leaf in NATURE of March 15 as to the interpretation of a passage of Strabo, the fact may possibly be of some interest that in the island of Mors, in Denmark, bricks are made from a local sandy clay which, after burning, float in water. These bricks are used, I understand, both as a refractory material and for ordinary building purposes … Their mechanical strength is said to be considerable. The porosity is not obtained by the addition of combustible or volatile matter during moulding. If the expression πηγνυμενας, used by Posidonius, be consistent with a process of burning the clay into bricks, and if clays of somewhat similar physical character to that of Mors … occur in Asia Minor and Spain, an explanation of the passage might perhaps be found in this direction.

From *Nature* 5 April 1917