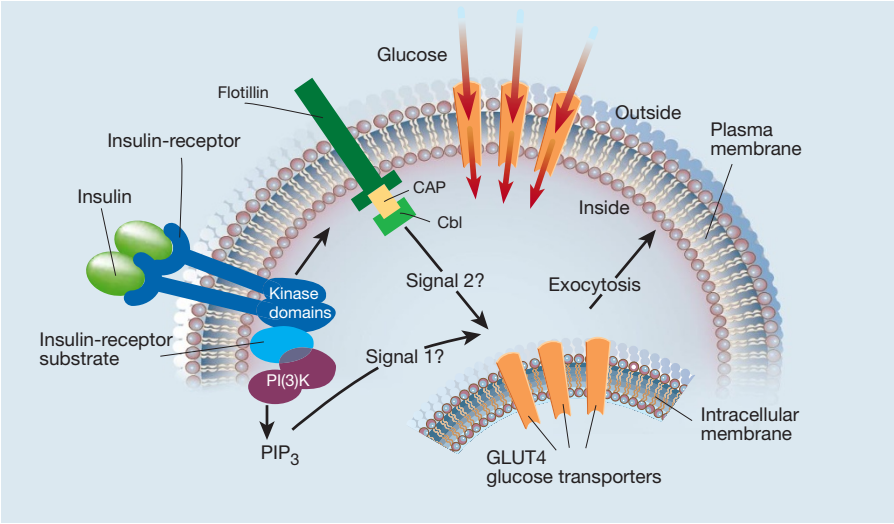


Figure 1 **Pathways for glucose uptake in muscle and fat cells. When insulin binds to its receptor on the cell surface, intracellular membranes containing the glucose transporter GLUT4 are induced to fuse with the plasma membrane (exocytosis), allowing the cell to take up glucose. There may be two pathways by which the insulin signal is transmitted to the GLUT4-bearing membranes inside the cell. Both pathways start with the phosphorylation of key substrates by the activated insulin receptor. One pathway, signal 1, involves the phosphorylation of insulin-receptor substrates and then the recruitment to them of phosphatidylinositol-3-OH kinase (PI(3)K). PI(3)K generates phosphatidylinositol-3,4-5-trisphosphate ($PIP_3$), a membrane lipid, which signals through unknown downstream effectors to regulate GLUT4. The results of Baumann *et al.*[2] indicate that the second pathway (signal 2) may involve the recruitment of flotillin–CAP–Cbl complexes to particular regions in the plasma membrane.**

mysteries of insulin signalling to GLUT4 is the molecular basis of its remarkable tissue specificity, as it occurs in only muscle and fat. Even when GLUT4 and insulin receptors are artificially placed in other cell types, insulin does not stimulate GLUT4 movement to the plasma membrane. This phenomenon, and the fact that Cbl is not tyrosine-phosphorylated in these other cell types, could be explained by the lack of CAP in these cells.

The connection of the flotillin–Cbl–CAP complexes to cholesterol-rich caveolae or lipid raft domains in the plasma membrane of cultured adipocytes is also intriguing. Insulin receptors may be associated with caveolae, a connection that might enhance insulin signalling[9]. And one of the substrates for PI(3)K, phosphatidylinositol-4,5-bisphosphate (from which $PIP_3$ is generated), is apparently concentrated in cholesterol-enriched domains of the plasma membrane. Although preliminary and fragmentary at present, these observations might reflect the coordinated localization of several signalling pathways involved in GLUT4 regulation.

But, like many odd discoveries, these results raise questions. For example, analysis of human Cbl and its nematode and fruitfly counterparts indicates that its main function in other cell types may be to dampen signalling from receptor tyrosine kinases. It does so by promoting a pathway by which the receptors are degraded after being activated by ligands[10]. So why doesn't Cbl also restrain the insulin-receptor tyrosine kinase, rather than seeming to promote its signalling? Does the truncated Cbl protein modulate GLUT4 transport, too? There are two other forms of mammalian Cbl; can they compensate for each other?

Perhaps the most important question is whether the complex discovered by Baumann *et al.* actually signals in response to insulin (Fig. 1), or whether it simply provides a constitutive, background activity required in some other way for GLUT4 regulation. It is still possible that the PI(3)K signalling pathway is the only one that needs to be activated by insulin. Either way, there are a lot of molecular details to be worked out. For example, does CAP function through signalling proteins known to be recruited to Cbl, or through proteins that have not yet even been discovered? If the history of studying insulin is any indication, the answers will provide us with yet more questions. ■

*Michael P. Czech is in the Program in Molecular Medicine and the Department of Biochemistry and Molecular Biology, 373 Plantation Street, University of Massachusetts Medical School, Worcester, Massachusetts 01605, USA.*
*e-mail: michael.czech@umassmed.edu*

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**Daedalus**

## Vitamins and minerals

**Bottled mineral water, says Daedalus, is a pretentious adjunct to modern living. It is mainly water with a bit of fizz, but each bottle lovingly details its mineral analysis. Sometimes it lists traces of beneficial substances such as calcium or magnesium; often it records ones which are definitely harmful, such as sodium. But the implied magic of bottled water lies in its origin — some special spring or source far from urban contamination. One brand even claims to have been melted from glaciers laid down centuries ago. Oddly enough, the magic of mineral water (unlike its chemical composition) fades rapidly. Almost all bottles have a well-marked sell-by date. Consumers of this potent elixir gladly pay the vast price demanded for it. It lets them avoid alcohol in restaurants and pubs without appearing too poor or too mean to pay lavishly for a drink.**

**Daedalus now plans to lend a little scientific credibility to this profitable product. He notes the vast trade in mineral and vitamin supplements. Logically, these are quite a cheap form of health insurance. Vitamin deficiencies can sometimes occur; and the lack of elements such as selenium and zinc can cause medical problems in susceptible people. And coronary heart disease, at least in Britain, seems to occur more in regions with soft water. Hard water, containing calcium and magnesium, may have a significant protective effect.**

**So DREADCO's 'Reinforced Water' (slogan: *Harder than hard!*) will combine the chic, magic and high price of mineral water with the genuine benefits of diet supplements. Its main active ingredients will be calcium and magnesium, of which we need about 0.8 gram and 0.3 gram a day respectively, and vitamin C, of which 0.1 gram a day is not excessive but which is unpleasantly acid. To force these palatably into solution, Reinforced Water will be pressurized with several atmospheres of carbon dioxide. It will then take up calcium and magnesium copiously as bicarbonates, and vitamin C as neutral calcium ascorbate. The other vitamins and minerals, needed in mere milligrams or less, should dissolve easily.**

**Smart, vigorously fizzy, powerfully healthful, but free of the pharmaceutical overtones of diet-supplement pills, Reinforced Water should dominate the mineral-water market. But dare DREADCO abandon mineral magic for mere scientific rigour? The company's marketeers are thinking of claiming that it issues from a spring on Mount Olympus, home of the Immortals.** **David Jones**