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Rosy prospect? A compound found in red wine might help to protect against the health problems associated with obesity.

A votre santé: now in pill form?

David Sinclair believes resveratrol is a miracle drug. He's been taking it for three years because he hopes it will help him live a healthier life, despite a lack of evidence that it works in humans — or any data on the safety of long-term exposure.

But this week, Sinclair comes a step closer to proving that he's on to something. He and his colleagues report in a paper published online in *Nature*[1] that this compound counteracts the ill effects of a high-fat, high-calorie diet — at least in mice. To some scientists, the finding has the whiff of a landmark discovery: it could lay the foundations for a future drug that blocks the toxic effects of obesity in humans. But how solid is that foundation?

The research is certainly striking. The study was led by Sinclair, of Harvard Medical School in Cambridge, Massachusetts, and Rafael de Cabo of the National Institute on Aging in Baltimore, Maryland. Their team divided one-year-old mice into three groups. One group ate regular food. Another ate high-calorie food. The third group ate the high-calorie diet along with a daily dose of resveratrol, a chemical found in many plant species, including red grapes — and thus also red wine.

After six months, all the mice fed high-calorie diets had grown fat. But after a year the mice in the resveratrol group seemed a lot healthier than their high-calorie-fed counterparts. The drug seemed to prevent these mice from developing a diabetes-like illness and liver damage, and reduced their risk of death by 30%, compared with the mice on high-calorie diets that did not get the drug.

That's a potentially revolutionary finding. But for those desperate to undo the effects of years of overeating, it is a far cry from a human cure. First, the study doesn't attempt to show whether resveratrol reverses the damage caused by the toxic diet, as the mice were on the drug when they started the diet. The equivalent experiment would be to feed a human a relatively healthy diet until middle age, and then force him or her to binge on Big Macs and resveratrol simultaneously.

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Second, there is a dearth of data on how resveratrol works in mice — and no evidence that it works at all in humans. Sinclair believes that it triggers the same pathways as those activated by calorie-restriction diets, which have been shown to increase lifespan in some animals (but not in humans, yet). He hypothesizes that resveratrol works through proteins called sirtuins. But although there are data to prove this in yeast, worms and fruitflies, no analogous data have proved it for humans or mice — despite tantalizing hints. So it is hard to know how well resveratrol's benefits will apply in people.

A third caveat is that mice on resveratrol didn't exactly mimic people on calorie-restriction diets. The mice stayed fat, for instance, and their cholesterol levels were far higher than those of mice on the standard diet. This means either that Sinclair and de Cabo decoupled obesity from its downstream ill-health effects or that resveratrol doesn't really mimic calorie restriction in mammals. Of course, the mechanism isn't so important if the drug works. But it means that, for now, experts are cautioning against the idea of rushing to an Internet pharmacy to buy resveratrol[2]. It is a dicey idea to take lifelong doses of a drug without having a clue about its mechanism of action or its long-term effects on the body.

Finally, although the study itself is robust as published, the analysis involves only 121 mice, many of which are still alive — the experiment isn't truly over until all the mice have died. Further studies by the same group will look at whether resveratrol extends lifespan in the healthy mice, too. Until all these results are in, we don't really have a complete picture of the drug's effects in obese and normal mice.

Even so, Sinclair is forging ahead to answer some of these questions. He is a co-founder of Cambridge-based Sirtris Pharmaceuticals, which aims to develop drugs that act on sirtuins. This summer, Sirtris tested a modified version of resveratrol in 85 healthy men. The company said on 4 October that it saw no ill effects of the drug in these volunteers, so it has now begun a clinical trial in 90 patients with diabetes. ■

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1. Baur, J. A. *et al. Nature* doi:10.1038/nature05354 (2006).
2. Kaeberlein, M. & Rabinovitch, P. S. *Nature* doi:10.1038/nature05308 (2006).