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## SCIENCE – IN THE NEWS

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### Obesity: Do Grapes Hold the Answer?

**R**esveratrol, a small polyphenol, has recently been shown to protect mice from many detrimental effects of diet-induced obesity (1,2). Treated animals are less prone to develop fatty liver or insulin-resistance, have improved motor coordination, and survive nearly as long as lean control animals despite persistent obesity. At higher doses, weight gain is significantly attenuated. Moreover, resveratrol improves aerobic capacity, endurance, and cold tolerance, suggesting that its protective effects are associated with general improvements in metabolism and increased energy expenditure. By many measures, mice fed a high-fat diet plus resveratrol appear as healthy as their lean counterparts.

So how does it work? The jury is still out, but to date the data seems to implicate sirtuins, a highly conserved class of NAD<sup>+</sup>-dependent deacetylases that control lifespan in lower organisms. Resveratrol activates sirtuins *in vitro*, and extends lifespan in yeast, worms, and flies in a sirtuin-dependent manner. In cultured cells, resveratrol stimulates SIRT1, the best-characterized mammalian sirtuin, to deacetylate and activate PGC-1 $\alpha$ , which is known to play important roles in glucose metabolism and mitochondrial biogenesis. Although other targets of SIRT1 may also be relevant to obesity, the activation of PGC-1 $\alpha$  provides a particularly attractive explanation for the multifaceted protective effects of resveratrol *in vivo*. Yet it must be pointed out that pharmacokinetic studies consistently show serum levels of resveratrol well below the *in vitro* ED<sub>50</sub> for SIRT1, and other putative mediators have not been excluded. Perhaps the most suggestive piece of evidence

linking SIRT1 to the beneficial effects of resveratrol is the demonstration that SNPs in the gene correlate with whole-body energy expenditure in humans.

Unraveling these mechanisms will likely lead to new therapeutic approaches down the road, but it's far too early to recommend megadoses of resveratrol for obese humans. Data from clinical trials establishing safety, let alone efficacy, is not yet available. Instead, the immediate message may be a very familiar one: eat your fruits and vegetables! Resveratrol is found in grapes, red wine, and other sources, and although dietary intake does not reach the levels used in the mouse studies, many structurally related molecules are present in other fruits and vegetables and may have additive, or even synergistic effects. These and other relatively unappreciated phytochemicals, even more than antioxidant capacity, may mediate the beneficial effects of consuming fresh produce, whether through SIRT1 or other unrecognized pathways. If the resveratrol studies are any indication, deficiency in dietary phytochemicals may severely compound the deleterious effects of obesity. These results should serve to highlight the importance of considering what is missing from the diet in obesity, in addition to what is in excess. – *Joseph A. Baur*

#### REFERENCES

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