Drug mimics low-cal diet to ward off weight gain, boost running endurance

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A drug designed to specifically hit a protein linked to the life-extending benefits of a meager diet can essentially trick the body into believing food is scarce even when it isn't, suggests a new report in the November *Cell Metabolism*.

The drug called SRT1720, which acts through the protein SIRT1, enhances running endurance in exercised mice and protects the animals against weight gain and insulin resistance even when they eat a high-fat diet, the researchers report. The drug works by shifting the metabolism to a fat-burning mode that normally takes over only when energy levels are low.

The findings bolster the notion that SIRT1 may be a useful target in the fight again metabolic disorders, including obesity and type 2 diabetes. It also helps lay to rest a long-standing controversy in the scientific world over the metabolic benefits of the red wine ingredient known as resveratrol. Resveratrol also acts on SIRT1, but its influence on other metabolic actors had left room to question exactly how it works.

" There has been a lot of controversy in the field about resveratrol action," said Johan Auwerx of Ecole Polytechnique Fédérale de Lausanne. "We find that the majority of the biology of resveratrol can be ascribed to SIRT1." While SIRT1 might not explain all of resveratrol's effects, the new results suggest that the central metabolic protein is responsible for about "80 percent of the picture," he said.

The researchers had conducted earlier studies to demonstrate many of the benefits of resveratrol. To further explore the underlying pathways responsible in the new study, they ran essentially the same experiments with the more potent and specific SIRT1-activating compound SRT1720 developed by the company Sirtris Pharmaceuticals, Inc.

The researchers found that a low dose of SRT1720 partially protected mice from gaining weight on a high-fat diet after 10 weeks of treatment. At higher doses, the drug completely prevented weight gain in the animals. SRT1720 also improved blood sugar tolerance and insulin sensitivity and endowed the animals with greater athletic ability.

" SIRT1720 made the animals run twice as long," Auwerx said. That improvement was seen only when the researchers specifically exercised the animals. Their voluntary activity actually declined in the study as they hunkered down to save energy.

They found further evidence that the SIRT1 activator acts as a calorie-restriction mimetic that favors the use of fat stores by promoting the direct modification of multiple SIRT1 targets. It also induces chronic metabolic adaptations that involve the indirect activation of AMPK, an enzyme that regulates skeletal muscle glucose and the metabolism of fatty acids.

The major advantage of SRT1720 or any specific SIRT1 activator over resveratrol is that it is likely to come with fewer side effects, Auwerx said.

That said, SRT1720 does have some limitations, Auwerx noted, in that the effects they observed came only at fairly high doses. He speculates that SRT1720 derivatives might get around this potential stumbling block for the drug's therapeutic promise.

While the researchers did not observe any significant side effects of the drug in their study, they said further studies are needed to adequately address that question.

Source: Cell Press