

Proteins linked to longevity may be involved in mood control

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(Medical Xpress) -- Over the past decade, MIT biologist Leonard Guarente and others have shown that very-low-calorie diets provoke a comprehensive physiological response that promotes survival, all orchestrated by a set of proteins called sirtuins.

In a [new paper](#) that appeared online in *Cell* on Dec. 8, Guarente and colleagues have now shown that [sirtuins](#) likely also play a key role in the [psychological response](#) to [dietary restriction](#). When sirtuins are elevated in the [brain](#), as occurs when [food intake](#) is cut, mice become much more anxious. Furthermore, in two large [genetic studies](#) of humans, the team found that mutations that boost production of sirtuins are commonly associated with higher rates of anxiety and [panic disorder](#).

The researchers believe that this anxiety may be an evolutionary adaption that makes animals — including humans — more cautious under the stressful condition of having to forage more widely for scarce food.

“It makes sense, because behavior effects would be as adaptive, and as selected by evolution, as physiological effects. I don’t think it’s surprising that behavior really falls under the umbrella of natural selection,” says Guarente, the Novartis Professor of Biology at MIT.

The research suggests that anxiety could potentially be treated with drugs that inhibit sirtuins. On the other hand, it also raises a caution when treating patients with drugs that activate sirtuins, several of which are

now in clinical trials for metabolic diseases, including diabetes. Those drugs can't enter the brain, but some researchers are exploring the possibility of using sirtuin inhibitors to treat neurological disorders such as Alzheimer's disease. If such drugs were developed and approved, doctors might need to watch for anxiety as a possible side effect.

Most of the experimental studies were performed in Guarente's lab at MIT, while the genetic studies were done primarily by collaborators at Virginia Commonwealth University and the University of Lausanne in Switzerland. Lead author of the paper is Sergiy Libert, a postdoc in Guarente's lab.

About 20 years ago, Guarente was the first to discover that sirtuins prolong lifespan in yeast; since then, they have been shown to have similar effects in worms, mice and other animals. Sirtuins, normally turned on in response to stresses such as starvation or inflammation, coordinate a variety of hormonal networks, regulatory proteins and other genes, with a net effect of keeping cells alive and healthy.

"We always wondered whether there might a psychological component that goes along with this," Guarente says.

In the new Cell study, Guarente and his colleagues examined two groups of mice: some with elevated levels of sirtuin [protein](#) in their brains and some with none. To test the psychological consequences of these alterations, the mice were placed on a circular raised platform with two quadrants protected by a wall, and two unprotected quadrants. "Normal mice will spend a considerable amount of time venturing out into the unprotected region, and super-anxious mice tend to stay in the protected area," Guarente says.

The researchers found that the mice with abnormally high sirtuin levels spent much more time closer to the walls, suggesting they were more

anxious. But mice lacking sirtuin protein were much more adventuresome.

The team then investigated the cellular mechanism behind this phenomenon, finding that sirtuins help control levels of the neurotransmitter serotonin, long known to be critical for mood regulation. “We were very surprised to see that, but it also made it relatively easy for us to figure out the mechanism by which sirtuins were regulating mood,” Guarente says.

Low serotonin levels usually produce anxiety and depression. The researchers found that sirtuins reduce serotonin levels by activating monoamine oxidase, or MAO, an enzyme that breaks down serotonin. (MAO is the target of many antidepressant drugs, known as MAO inhibitors.)

The researchers also tested the mice for depression and found effects similar to anxiety, but “in [mice](#), the measures for depression are not as robust, so it’s a little bit harder to assess,” Guarente says.

Guarente’s lab then teamed up with researchers at the University of Lausanne who had identified mutations in the SIRT1 gene in humans associated with anxiety, panic disorder and social phobia. The two groups investigated the molecular consequences of some of those SIRT1 mutations, and found that they led to sirtuin overactivity. Another group of collaborators at Virginia Commonwealth University found a strong correlation between one of those SIRT1 [mutations](#) and the risk of panic disorder.

This suggests that people on very-low-calorie diets might also feel more anxious, because their brains would be producing more sirtuins. However, Guarente says he knows of no studies that have investigated this.

Recent studies have suggested that sirtuin activators may prove useful in treating neurological disorders such as Alzheimer's and Parkinson's. To treat those diseases, these drugs would need to be able to cross the blood-brain barrier, which keeps most molecules circulating in the bloodstream from entering the brain. Such drugs could produce anxiety as a side effect, but are still worth pursuing, Guarente says.

“What we want to do is we want to learn as much as we can about the biology of sirtuins, to inform the use of sirtuin drugs to treat diseases. The more we know about the biology, the better position we'll be in to know how to use the drugs, how to dose them and how to anticipate any possible side effects,” he says. “I think most people would be willing to trade a therapeutic for a debilitating disease like Alzheimer's for an increase in [anxiety](#), which could be treated secondarily with a selective serotonin reuptake inhibitor such as Prozac.”

Provided by Massachusetts Institute of Technology

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