

Blocking pain receptors found to extend lifespan in mammals

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Credit: Martha Sexton/public domain

Blocking a pain receptor in mice not only extends their lifespan, it also gives them a more youthful metabolism, including an improved insulin response that allows them to deal better with high blood sugar.

"We think that blocking this pain receptor and pathway could be very,

very useful not only for relieving pain, but for improving lifespan and metabolic health, and in particular for treating diabetes and obesity in humans," said Andrew Dillin, a professor of molecular and cell biology at the University of California, Berkeley, and senior author of a new paper describing these results. "As humans age they report a higher incidence of pain, suggesting that pain might drive the aging process."

The "hot" compound in chili peppers, capsaicin, is already known to activate this pain receptor, called TRPV1 (transient receptor potential cation channel subfamily V member 1). In fact, TRPV1 is often called the capsaicin receptor. Constant activation of the receptor on a nerve cell results in death of the neuron, mimicking loss of TRPV1, which could explain why diets rich in capsaicin have been linked to a lower incidence of diabetes and metabolic problems in humans.

More relevant therapeutically, however, is an anti-migraine drug already on the market that inhibits a protein called CGRP that is triggered by TRPV1, producing an effect similar to that caused by blocking TRPV1. Dillin showed that giving this drug to older mice restored their metabolic health to that of younger mice.

"Our findings suggest that pharmacological manipulation of TRPV1 and CGRP may improve metabolic health and longevity," said Dillin, who is a Howard Hughes Medical Institute investigator and the Thomas and Stacey Siebel Distinguished Chair in Stem Cell Research. "Alternatively, chronic ingestion of compounds that affect TRPV1 might help prevent metabolic decline with age and lead to increased longevity in humans."

Dillin and his colleagues at UC Berkeley and The Salk Institute for Biological Studies in La Jolla, Calif., will publish their results in the May 22 issue of the journal *Cell*.

Pain and obesity

TRPV1 is a receptor found in the skin, nerves and joints that reacts to extremely high temperatures and other painful stimuli. The receptor is also found in nerve fibers that contact the pancreas, where it stimulates the release of substances that cause inflammation or, like CGRP (calcitonin gene-related peptide), prevent insulin release. Insulin promotes the uptake of sugar from the blood and storage in the body's tissue, including fat.

Past research has shown that mice lacking TRPV1 are protected against diet-induced obesity, suggesting that this receptor plays a role in metabolism. Disrupting sensory perception also increases longevity in worms and flies. But until now, it was not known whether sensory perception also affects aging in mammals.

Dillin and his team have now found that mice genetically manipulated to lack TRPV1 receptors lived, on average, nearly four months – or about 14 percent – longer than normal mice. The TRPV1-deficient mice also showed signs of a youthful metabolism late in life, due to low levels of CGRP—a molecule that blocks insulin release resulting in increased blood glucose levels and thus could contribute to the development of type 2 diabetes. Throughout aging, these mice showed improved ability to quickly clear sugar from the blood as well as signs that they could burn more calories without increasing exercise levels.

Moreover, old mice treated with the anti-migraine drug, which inhibits the activity of CGRP receptors, showed a more youthful metabolic profile than untreated old mice.

UC Berkeley and The Salk Institute filed a patent May 16 on the technology described in the *Cell* paper. Dillin plans to continue his studies of the effects of TRPV1 and CGRP blockers on mice and, if possible, humans.

More information: *Cell*, Riera et al.: "TRPV1 Pain Receptors Regulate Longevity and Metabolism by Neuropeptide Signaling."
[http://www.cell.com/cell/abstract/S0092-8674\(14\)00481-4](http://www.cell.com/cell/abstract/S0092-8674(14)00481-4)

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