NEUROENDOCRINOLOGY

A long pain-free life

Chronic pain has previously been shown to be linked with a decrease in lifespan; however, the pathways and molecular mechanisms underlying this association are still unclear. A new study by Riera *et al.* in mice and *Caenorhabditis elegans* now reveals a novel neuroendocrine pathway in which the activation of transient receptor potential cation channel subfamily V member 1 (TRPV1), which is pain-sensitive, regulates metabolism, with negative consequences for longevity.

The authors discovered that mice that lacked TRPV1 lived 100–130 days longer than their wild-type (WT) counterparts. Moreover, whereas WT mice showed a decline in their metabolic capacity with age, old *Trpv1*^{-/-} mice retained a more youthful metabolism — they maintained a more efficient circadian transitioning between glucose and lipid metabolism, and a higher oxygen consumption rate. Glucose- and insulin-tolerance tests revealed that *Trpv1*^{-/-} animals were not hyper-insulinaemic, but they did release more insulin following glucose challenge than did WT mice, possibly explaining their altered metabolism.

To elucidate how the mice that lacked TRPV1 maintained a youthful metabolic profile, the authors used various mutant strains of *C. elegans*. Worms with null mutations in two genes encoding TRPV family members (TRPV mutants) lived approximately one-third longer than WT worms. Similarly, RNAi-mediated inactivation of *tax-6*, the worm orthologue of the phosphatase calcineurin, also extended lifespan. However, inactivation of *tax-6* in the (already long-lived) TRPV mutants did not

further extend longevity, leading the authors to conclude that TRPVs may function upstream of calcineurin.

Calcineurin is known to dephosphorylate CREB-regulated transcription co-activator 1 (CRTCl), resulting in the trafficking of CRTCl from the cytosol into the nucleus. TRPV mutant worms that expressed a mutant form of CRTCl that was constitutively nuclear had a normal lifespan. Moreover, in WT mouse dorsal root ganglion (DRG) neurons, activation of TRPV1 with capsaicin (a natural TRPV1 agonist) led to shuttling of cytosolic CRTCl to the nucleus; however, this capsaicin-induced trafficking of CRTCl was abrogated in *Trpv1*^{-/-} neurons. Together, these data indicate that in WT neurons, TRPV1 activity promotes the localization of CRTCl to the nucleus.

Trpv1^{-/-} mouse DRG neurons had reduced mRNA levels for various CRTCl-induced genes, including the gene encoding calcitonin gene-related peptide (CGRP). Incubation of pancreatic β -cells with recombinant CGRP reduced the glucose-stimulated release of insulin. Strikingly, whereas in WT mice circulating levels of CGRP increased markedly with age, CGRP levels in *Trpv1*^{-/-} mice remained low even in older animals. Furthermore, unlike vehicle-treated aged mice, old WT mice that were treated with a CGRP antagonist for 6 weeks showed youthful metabolic profiles that were similar to those of old *Trpv1*^{-/-} mice. These results imply that activated TRPV1-positive DRG neurons release CGRP onto the pancreas and inhibit β -cell release of insulin.

In summary, this study provides evidence that pain-sensitive sensory neurons in the DRG release CGRP, which could over time have long-term consequences on metabolism and longevity by reducing pancreatic release of insulin. These findings may have important implications with regard to age-associated type 2 diabetes and chronic pain disorders.

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This article originally appeared in *Nature Rev. Neurosci.*
(<http://dx.doi.org/10.1038/nrn3778>).

ORIGINAL RESEARCH PAPER Riera, E. *et al.*
TRPV1 pain receptors regulate longevity and metabolism by neuropeptide signaling. *Cell* **157**, 1023–1036 (2014)

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