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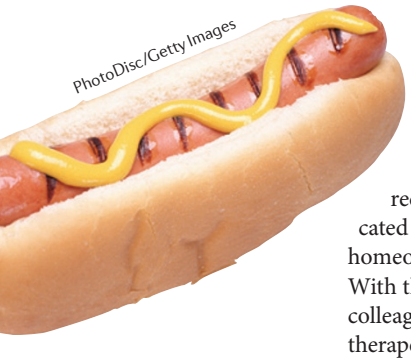
METABOLIC DISEASE

Potassium channel blocker prevents obesity

Pharmacological options for the treatment of obesity and its associated disorders are limited, and there is an urgent need for long-term effective and safe therapeutic approaches. Now, writing in *PNAS*, Chandy and colleagues demonstrate that inhibition of the voltage-gated potassium channel Kv1.3 has a powerful anti-obesity effect in mice.



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Kv1.3 has long been associated with immune regulation, and several inhibitors of the channel are currently in preclinical development for the treatment of autoimmune disease. However, more recently, Kv1.3 has been implicated in the regulation of energy homeostasis and body weight. With this in mind, Chandy and colleagues set out to investigate the therapeutic potential of a peptide inhibitor of KV1.3 — ShK-186 — in the treatment of metabolic disorders.

The authors first treated mice with ShK-186 via subcutaneous injection every other day, in conjunction with the initiation of an obesity-inducing diet (high fat and high fructose). After 45 days, in comparison with untreated mice, ShK-186-treated mice exhibited significantly reduced weight gain, adiposity and associated inflammation. In addition, the treated mice exhibited lower blood levels of cholesterol, glucose, insulin and leptin, and improved glucose tolerance and peripheral insulin sensitivity. Treatment with ShK-186 also significantly slowed weight gain in mice that had been fed an obesity-inducing diet for 3 weeks prior to initiation of therapy. Interestingly, ShK-186 had no effect in mice that were fed a regular diet.

Next, the authors set out to determine the mechanisms mediating the therapeutic benefits of ShK-186. They noted that ShK-186 increased glucose uptake by brown adipose tissue (BAT) — an important thermogenic tissue. In addition, global metabolic profiling of key genes revealed that ShK-186 induced significant metabolic changes in BAT — increasing β-oxidation of fatty acids, glycolysis, fatty acid synthesis and uncoupling protein 1 expression — which together indicated increased thermogenesis. Indeed, analysis of the metabolic status of mice treated with ShK-186 revealed a higher metabolic rate and increased energy expenditure compared to untreated mice, without changes in physical activity or calorie intake.

ShK-186 was also found to affect the liver of mice that were fed an obesity-inducing diet, where it heightened the activity of metabolic pathways involved in energy and lipid metabolism and reduced fat accumulation. Notably, Kv1.3 expression was increased three- to four-fold in the liver of these mice, which may partly explain the lack of effect of ShK-186 in mice that were fed a regular diet. Metabolic changes were also observed in white adipose tissue (WAT) following ShK-186 treatment but, given the absent or minimal expression of Kv1.3 in WAT, they are likely to be responses to changes in other tissues such as BAT and the liver.

Together, these results highlight the potential use of Kv1.3 blockers for the treatment of obesity and related metabolic disorders. Encouragingly, ShK-186 has been found to be well tolerated in a Phase I trial in autoimmune disease.

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ORIGINAL RESEARCH PAPER Upadhyay, S. K. *et al.* Selective Kv1.3 channel blocker as therapeutic for obesity and insulin resistance. *Proc. Natl. Acad. Sci. USA* **110**, E2239–E2248 (2013)