I’ve always wondered why my husband insists on growing hot peppers in the garden each year. Indeed if you pop 1 of these little bits of fire into your mouth the burning sensation that ensues is truly a memorable experience. But my husband always says that eating hot peppers is good for you. And indeed, he might be right. Hot peppers contain capsaicin, the chemical responsible for the “hot”,1,2 Capsaicin is used clinically for a number of indications including pain and itch relief and for some forms of rhinitis and headache.1 It has also been implicated in playing a role in prevention of colon cancer and in antimicrobial actions against Helicobacter pylori.3 Capsaicin is a potent agonist for the TRPV1 calcium channel.1,2 TRPV1 is perhaps best known as a “molecular integrator” of noxious or painful stimuli.4 However, physiological roles not associated with pain are now becoming evident for TRPV1. In this issue of Circulation Research, Zhang and colleagues present a novel, physiological role for the TRPV1 channel in the prevention of adipogenesis and obesity.5 Obesity is a major, global health concern. According to the World Health Organization,6 there were approximately 1.6 billion overweight adults in 2005, with at least 400 million obese people. The projections are even more staggering for the year 2015 with approximately 2.3 billion overweight adults and greater than 700 million obese people. Being overweight or obese increases the risk of developing numerous deleterious health conditions including heart disease, diabetes, cancer, arthritis, and reproductive problems.7 To reverse this epidemic, the general population must become proactive to reach and maintain a healthy body weight. To this end there are numerous over-the-counter products claiming to promote weight loss. Most of these products, however, come saddled with efficacy and safety concerns. It would be desirable to identify a safe and efficacious therapy to aid in weight loss and maintenance.

During the last decade numerous articles have been published linking human capsaicin intake to factors that would aid in weight loss and maintenance. Red pepper consumption was shown to increase energy expenditure and lipid oxidation8 as well as decrease appetite.9,10 Although the mechanisms underlying these effects are not fully understood, it has been proposed that capsaicin stimulates sensory neurons in the mouth and gastrointestinal tract resulting in increased noradrenaline levels.11 Findings from Zhang and colleagues now report a second mechanism through which capsaicin may aid in weight loss. Their work suggests that capsaicin activates a TRPV1 channel, and promotes calcium entry that is necessary to prevent preadipocyte-to-adipocyte differentiation. TRPV1 activation may ultimately reduce the number and size of fat cells, and therefore reduce the propensity for obesity to develop.

TRPV1 is a member of the transient receptor potential superfamily of proteins.12,13 It is a nonselective cation channel with high calcium permeability13 and is activated by noxious stimuli including chemicals in the vanilloid class (eg, capsaicin and resiniferatoxin), elevated temperatures and protons.4 TRPV1 is highly expressed in sensory neurons, but has also been detected in numerous other tissues including the brain, pancreas, kidney and liver.4 In the current study, Zhang et al detected TRPV1 for the first time in mouse embryo 3T3-L1 preadipocytes, as well as in human and mouse visceral adipose tissue.8 Induction of adipogenesis was accompanied by a concomitant decrease in TRPV1 expression and decreased capsaicin-mediated calcium influx. In the presence of capsaicin, TRPV1 downregulation was no longer observed, the capsaicin-induced cytosolic calcium increase was maintained, and adipogenesis was prevented. Surprisingly the prolonged capsaicin treatment (8 days) did not desensitize TRPV1 channels. The authors also performed in vivo studies in which mice fed a high fat diet in the presence of capsaicin exhibited lower body weight and higher TRPV1 expression compared with mice on a high fat diet alone. In TRPV1 knock-out mice there was no significant difference in body weight between mice on a high fat diet with or without capsaicin. Collectively, data in this study provide evidence for activation of TRPV1 and increased cytosolic calcium in the prevention of adipogenesis.

Activation of the TRPV1 channel by capsaicin leads to an increase in cytosolic calcium. Several studies have implicated a role for increased cytosolic calcium in the prevention of the early phases of adipogenesis. In 3T3-L1 preadipocytes, application of the plant alkaloid thapsigargin or the calcium ionophore A23187 to increase cytosolic calcium resulted in inhibition of the early phases of differentiation.14 In human adipocytes, increases in cytosolic calcium exhibited a biphasic effect in the regulation of differentiation.15 Increases in cytosolic calcium inhibited the early stages but enhanced the late stage of differentiation. Clearly then not all increases in cytosolic calcium lead to inhibition of adipocyte differentiation. Indeed, potential downstream calcium targets include both pro- and antiadipogenic factors. The question arises then, what regulates such divergent effects of calcium signaling on adipogenesis?
It is well recognized that diverse signaling events can be regulated by localization of signaling components to specific cellular microdomains. Lipid rafts and caveolae are cholesterol-rich membrane microdomains which are important for the coalescence of signaling partners into distinct areas of the cell. Functional TRPV1 channels, at least in nociceptors, appear to require localization to lipid rafts. On activation of the TRPV1 channel, calcium pools with elevated calcium concentrations could form in the vicinity of lipid rafts containing TRPV1. It is interesting to speculate that lipid raft microdomains play a role in regulation of calcium-mediated inhibition of adipogenesis.

Lipid raft and caveolae microdomains have been implicated in the localization of a number of ion channels including store-operated calcium (SOC) channels. SOC entry is a unique mechanism whereby calcium channels in the plasma membrane are activated in response to depletion of calcium from the endoplasmic reticulum. SOC entry channels also play a role in adipogenesis. Nuclear factor of activated T cells is a transcription factor that has been shown to promote the expression of the aP2 gene and adipocyte differentiation. Nuclear factor of activated T cells is known to be activated by the cell. And further, microdomains may play an important role in calcium-mediated inhibition of adipogenesis.

Model of how calcium pools associated with lipid raft microdomains might play a role in adipogenesis. TRPV1 channels and store-operated calcium (SOC) entry channels are localized to lipid microdomains. Activation of TRPV1 allows for calcium entry and the formation of a calcium pool. Calcineurin nearby this calcium pool becomes activated and inhibits its proadipogenic transcription factors such as PPAR-γ and C/EBPα, leading to repression of adipogenesis. On the other hand, calcium depletion of the endoplasmic reticulum leads to activation of SOC entry channels. Some SOC entry channels provide the calcium source necessary to activate Nuclear factor of activated T cells (NFAT) in a calcineurin-dependent manner resulting in increased expression of proadipogenic factors such as a2 and facilitation of adipocyte differentiation. Although this model is simplistic, it emphasizes the point that specific microdomains can contribute to divergent physiological functions within the cell. And further, microdomains may play an important role in calcium-mediated inhibition of adipogenesis.

Inhibition of adipogenesis and obesity through activation of TRPV1 by its agonist capsaicin is an exciting prospect. Data presented by Zhang et al provide compelling evidence supporting this idea, yet they also reveal some unresolved questions. To begin, negative feedback mechanisms have been reported for sensory neurons, where prolonged or elevated capsaicin treatment leads to desensitization of TRPV1 channels. In the gastrointestinal tract afferent neurons which are sensitive to capsaicin contribute to regulation of nociception, circulation, mucosal homeostasis, motility and secretion. It will be critical then to determine whether TRPV1 in neurons of the gastrointestinal tract is desensitized by levels of capsaicin required to inhibit adipogenesis, as this could lead to disturbances in normal gastrointestinal function. In addition, as TRPV1 has also been detected in numerous cell types including endothelial cells and smooth muscle cells, the downstream effects resulting from activation, and possibly desensitization, of other capsaicin-sensitive TRPV1 channels must be considered. Finally, a critical question regarding the normal physiological regulation of preadipocyte-to-adipocyte differentiation remains: what are the endogenous agonists and antagonists of preadipocyte TRPV1 channels important for regulation of adipogenesis? Considering that TRPV1 is susceptible to sensitization one could speculate that capsaicin is playing a role in sensitizing the TRPV1 channel to its endogenous agonist. As these and other issues become clearer, it may indeed turn out that capsaicin-mediated activation of TRPV1 is an enticing way to prevent obesity.

Sources of Funding

D.C. is funded by grant number 0625311B from the American Heart Association.

Disclosures

None.
References


Key Words: TRPV1 / capsaicin / adipogenesis / obesity / microdomains
The Skinny on TRPV1
Donna L. Cioffi

Circ Res. 2007;100:934-936
doi: 10.1161/01.RES.0000265139.10277.62
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
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