Transient Receptor Potential Vanilloid Type-1 Channel in Cardiometabolic Protection

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▌ ABSTRACT ▐ ────────────────────────────────

Transient receptor potential vanilloid type-1 channel (TRPV1) is a non-selective cation channel with a preference for calcium ions that is able to sense a vast range of endogenous physical and chemical stimuli and plays an important role in transducing the sensations of noxious heat and pain signaling. Recent studies showed that TRPV1 is widely expressed in different tissues and organs beyond the sensory nerves and has multiple biological effects that are involved in functional regulation in the pancreas, blood vessel, adipose tissue and liver. To further understand the link between TRPV1 and cardiometabolic diseases, we reviewed the role of TRPV1 in hypertension, diabetes, obesity, and dyslipidemia. This review provides new insights into the involvement of TRPV1 channels in the pathogenesis of cardiometabolic disorders and implicates this channel as a potential therapeutic target for the management of cardiometabolic diseases.

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Key Words: Transient receptor potential channel vanilloid type 1; Capsaicin; Cardiometabolic disease

Introduction

Cardiovascular disease (CVD) remains by far the leading cause of morbidity and mortality in the world.[1,2] Risk factors for CVD and type 2 diabetes often cluster, including abdominal obesity, hypertension, insulin resistance, hyperglycemia, and dyslipidemia, and are called cardiometabolic risk factors (CMRFs).[3,4] When occurring together, CMRFs increase a patient's chance for developing diabetes, heart disease, or stroke. Modifications of CMRFs seem to have a beneficial effect on clinical outcomes, but management guidelines for CMRFs are still not available at the present time.

For managing both long- and short-term risk, lifestyle therapies are the first-line interventions to reduce the cardiometabolic risk factors. In the American Heart Association 2006 Diet and Lifestyle Recommendations for Cardiovascular Diseases Risk Reduction, it was recommended to balance caloric intake; consume a diet rich in vegetables and fruits; choose whole-grain, high-fiber foods; consume oily fish, low salt and high potassium; and limit intake of saturated fat and beverages and foods with added sugars.[5] A recent report showed that a reduction of salt (3 g per day) lowered blood pressure 4–6 mm Hg in the entire study population and 6–9 mm Hg in African Ameri-

cans. Reducing dietary salt by 3 g per day is projected to reduce the annual number of new cases of coronary heart disease (CHD), stroke, and myocardial infarction. This benefit is similar to the administration of anti-hypertensive drugs or statins.[6]

Capsaicin is the pungent ingredient in hot chili peppers. Recently, some evidence showed that chronic treatment of red peppers can decrease abdominal fat and increase fat oxidation, and long-term consumption of spicy foods decreased the incidence of cardiovascular events.[7-9] In recent years, our studies showed that dietary capsaicin, acting as a transient receptor potential vanilloid type-1 channel (TRPV1) agonist, can prevent obesity and lower blood pressure in spontaneous hypertensive rats (SHR).[10,11] This evidence implicates capsaicin as a potential therapeutic agent for the management of cardiometabolic diseases.

The target for capsaicin is the capsaicin receptor, also called TRPV1. TRPV1 was first cloned by David Julius in 1997.[12] This channel is a member of the TRP superfamily and a nonselective cation channel with high calcium permeability; it has six transmembrane domains and a short, pore-forming hydrophobic stretch between the fifth and sixth transmembrane domains.[13] Capsaicin binding to TRPV1 triggers an increase in intracellular calcium, which causes the release of several neuropeptides, such as substance P and calcitonin gene-related peptide (CGRP).[14] When this occurs in sensory nerves, it promotes the sensation of pain, inflammation, and of the local heat. TRPV1 is also activated by noxious heat (> 43°C) and acid (pH < 5.9), voltage, and various lipids (Fig. 1). Experiments have demonstrated that TRPV1 is widely expressed in different tissues and organs beyond sensory nerves, such as pancreas, blood vessels, adipose tissue and liver, and is well recognized to play roles in pain sensation and thermosensation, apoptosis, regulation of bladder function, taste, and neurogenic inflammation.[13,15] Recent emerging evidence shows that TRPV1 plays an important role in
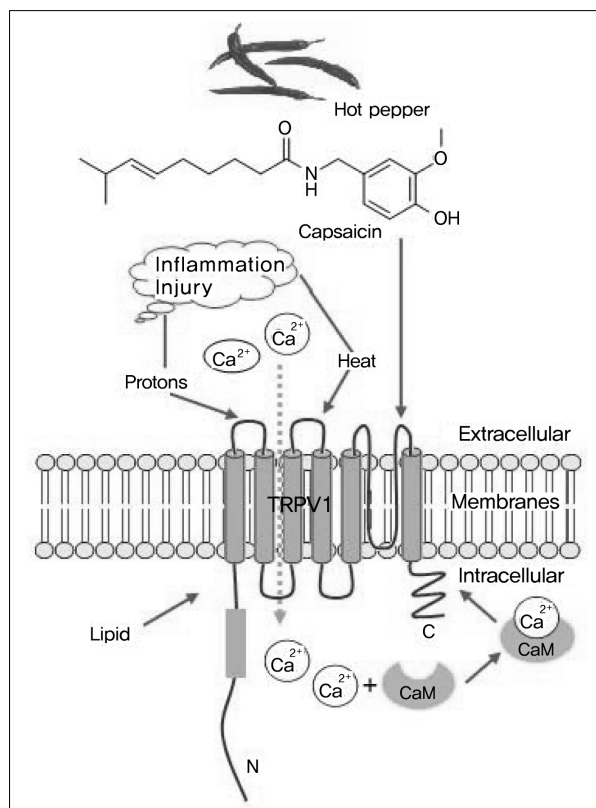

Fig. 1. Transient receptor potential vanilloid type-1 channel (TRPV1) has six transmembrane domains and a short, pore-forming hydrophobic stretch between the fifth and sixth transmembrane domains. Capsaicin binding to TRPV1 triggers an increase in intracellular calcium. When this occurs in sensory nerves, it promotes the sensation of pain, inflammation, and local heat. TRPV1 is also activated by noxious heat (> 43°C) and acid (pH < 5.9), voltage, and various lipids.

metabolic regulation and vascular function and exerts beneficial effects on cardiometabolic diseases. In this review, we will focus on its role in cardiometabolic diseases.

TRPV1 and vascular tone

TRPV1 channels are densely distributed in the myocardium and the circulatory system, not only in sensory nerves but also in other cell types, such as the vascular smooth muscle cells and endothelial cells.[10,16,17] Data from both animal models and patients indicate that TRPV1 channels play an important role in regulating vascular tone.

It is well known that capsaicin-sensitive sensory nerves

play a significant role in controlling the vascular tone through the release of CGRP, substance P (SP), and neu-rokinin A.[18] Among the vasodilators, CGRP is believed to play an important role.[19,20]

White et al.[21] found capsaicin dilated arterioles, and CGRP caused dilation similar to capsaicin. Pretreatment with a CGRP inhibitor prevented resiniferatoxin- and cap-saicin-induced dilation. These results suggest that cap-saicin can dilate microvessels by releasing CGRP, which can modulate tone. SP also caused vasodilatation of the pre-contracted arteries, but this effect was transient, and tachyphylaxis developed rapidly upon repeated admini-stration. Incubation with the CGRP fragment (8-37) abol-ished the vasodilatation induced by resiniferatoxin and capsaicin, while leaving the effect of neurokinin A and SP unaltered.[18] Li and Wang[22] demonstrated that capsaicin can affect cardiovascular function by stimulating the re-lease of CGRP and SP from perivascular sensory nerve endings, and the CGRP-independent mechanism also par-tially accounts for the vasodilatation effect.[22] These results implicated that capsaicin, as an agonist of TRPV1 chan-nels, causes the release of CGRP, whereas SP plays a neu-rotransmitter role in capsaicin-sensitive vasodilator nerves.

Activation of TRPV1 channels causes the production of NO in endothelial cells, leading to vasorelaxation. Poblete et al. found the NO release elicited by capsaicin was re-duced by the TRPV1 receptor antagonists, as well as by the cannabinoid CB1 receptor antagonists.[23] The outflow of NO elicited by capsaicin was also reduced by endothe-lium removal or NOS inhibition, suggesting the specific participation of endothelial TRPV1 receptors.[23] In lean pigs, capsaicin relaxed coronary arteries in a dose-depend-ent manner. This relaxation was blocked by the TRPV1 antagonist capsazepine, endothelial denudation, or in-hibition of NOS.[24] Capsaicin elicited a divalent cation in-flux that was abolished in endothelial cells from obese pigs, indicating that TRPV1 mediates endothelium-de-

pendent vasodilatation through a mechanism involving NO, and impaired capsaicin-induced vasodilatation in the metabolic syndrome is associated with decreased ex-pression of TRPV1 and cation influx.[24] We recently re-vealed a link between the TRPV1 and blood vessel func-tion, as TRPV1 activation by capsaicin enhances endothe-lium-dependent relaxation in wild-type mice, an effect ab-sent in TRPV1-deficient mice. Chronic TRPV1 activation by dietary capsaicin increases the phosphorylation of pro-tein kinase A (PKA) and eNOS and thus production of NO in endothelial cells, which is calcium dependent. Long-term stimulation of TRPV1 can activate PKA, which contributes to increased eNOS phosphorylation and im-proves vasorelaxation.[10] We also demonstrated that chron-ic dietary capsaicin reduced high-salt diet-induced endo-thelial dysfunction in part by preventing the generation of superoxide anions and NO reduction of mesenteric arteries through vascular TRPV1 activation.[25] This evidence in-dicates that activation of TRPV1 may stimulate the release of CGRP from capsaicin-sensitive sensory nerves, increase the phosphorylation of PKA and eNOS and thus the pro-duction of NO from endothelial cells, and play a critical role in vascular tone regulation.

TRPV1 and hypertension

A change of peripheral vascular resistance is a key fac-tor regulating blood pressure. As described before, vaso-constrictors and vasodilators from sympathetic and cap-saicin-sensitive sensory nerves play important roles in reg-ulating blood pressure.[19] Recent studies have shown that the TRPV1 channel is associated with the pathogenesis of hypertension.[26] Activation of TRPV1 has been shown to exert antihypertensive effects through stimulating the re-lease of CGRP from capsaicin-sensitive sensory nerves or NO from endothelial cells.

It has been shown that plasma concentrations of CGRP

rise transiently after acute administration of capsaicin in adult rats accompanied by a decrease in blood pressure.[19] Hypotensive effects were also obtained with the administration of TRPV1 endogenous ligand anandamide, which were almost completely prevented in the presence of capsazepine, the antagonist of TRPV1.[27] Rutaecarpine, a major active component of the Chinese herbal drug Tetradium ruticarpum, was able to stimulate the release of CGRP by activation of TRPV1. Drugs based on Tetradium ruticarpum have been widely used in China for hundreds of years to treat hypertension.[28] As mentioned before, we revealed another way activation of TRPV1 lowers blood pressure. TRPV1 activation increases the phosphorylation of PKA and eNOS and thus production of NO in endothelial cells, a process that is calcium-dependent. Long-term stimulation of TRPV1 by dietary capsaicin lowers blood pressure in SHR.[10]

TRPV1 channels are also involved in the regulation of sodium excretion, which is critical for the control of blood pressure, especially in cases of salt-sensitive hypertension. Wang et al.[29] found that high salt (HS) intake increased baseline mean arterial pressure. Capsazepine, a selective TRPV1 antagonist, caused a greater increase in blood pressure in HS-treated compared to normal salt (NS)-treated rats. HS intake increases production of anandamide, which may serve as an endovanilloid to activate TRPV1, leading to the release of CGRP to blunt salt-induced increases in blood pressure. These data support the notion that TRPV1 may act as a molecular target for salt-induced elevation of endovanilloid compounds to regulate blood pressure. TRPV1 receptor is activated and its expression upregulated during HS intake in Dahl salt-resistant (DR) rats, which acts to prevent salt-induced increases in blood pressure. In contrast, TRPV1 expression and function are impaired in Dahl salt-sensitive (DS) rats, which renders DS rats sensitive to salt load in terms of blood pressure regulation. Our data revealed consumption of a HS diet elevated nocturnal blood pressure in mice. These effects were associated with increased superoxide anion generation and reduced NO levels in mesenteric vessels in mice on a HS diet. Chronic dietary capsaicin reduced nocturnal hypertension, in part, by preventing the generation of superoxide anions and NO reduction of mesenteric arteries through vascular TRPV1 activation.[25]

TRPV1 and cardiac protection

Activation of TRPV1 exerts beneficial effects on an ischemic myocardium. Alison et al. used male Wistar rat hearts perfused in the Langendorff mode and found that infusion of 12-lipoxygenase (12-LOX) and arachidonic acid (AA) reduced infarct size and improved left ventricular-developed pressure after ischemia/reperfusion (I/R) insult. The protection was abolished by the 12-LOX inhibitor baicalein or by treatment of animals with a high dose of capsaicin, supporting a role for sensory C-fibers in 12-LOX-mediated cardioprotection.[30] Cardiac TRPV1 mRNA levels were significantly reduced and protein expression elevated in a similar *in vivo* model. Additionally, in dorsal root ganglia (DRG), TRPV1 mRNA was unchanged, whereas protein levels were elevated. Together, these data suggest that I/R injury results in a decrease in TRPV1 expression locally within the heart, but an increase of TRPV1 synthesis in DRG and transport to cardiac nerve terminals occur *in vivo* to maintain expression levels. Moreover, during I/R injury upregulation/activation of the 12-LOX/AA/TRPV1 pathway represents an endogenous damage-limiting mechanism.[30]

Some experiments implicated a cardiac protection effect of TRPV1 due to the release of neurotransmitters, such as CGRP and SP, from TRPV1-positive (TRPV1+) sensory nerves.[31,32] This cardioprotective effect provided by CGRP- or capsaicin-induced preconditioning was abolished by CGRP-(8-37), a selective CGRP receptor antagonist. It

has been shown that the protective effects of endogenous CGRP rely on the intact function of capsaicin-sensitive sensory nerves because a high dose of capsaicin pretreatment, which selectively depletes transmitters in capsaicin-sensitive sensory nerves, could abolish the protective effects of CGRP.[31] Huang et al.[33] demonstrated that TRPV1 gene deletion results in excessive inflammation, disproportional left ventricular remodeling, and deteriorated cardiac function after myocardial infarction, indicating that TRPV1 may prevent infarct expansion and cardiac injury by inhibiting inflammation and abnormal tissue remodeling. TRPV1 contributes to the cardioprotective effect of ischemic preconditioning (IPC) against I/R injury also associated with the release of CGRP and SP.[34] Cardioprotection by IPC against I/R injury is lost in TRPV1–/– hearts, and the underlying mechanism is partly associated with the decreased CGRP and SP release due to the impairment of TRPV1 receptor.[34]

TRPV1 and diabetes

Much evidence shows that TRPV1 associated with the diabetic process plays an important role in the regulation of plasma glucose levels. Akiba et al.[35] demonstrated for the first time that TRPV1 is functionally expressed in rat islet β cells and plays a role in insulin secretion as a calcium channel. Capsaicin dose-dependently increased insulin secretion from RIN cells, and this effect was inhibited by either a TRPV1 inhibitor capsazepine or EDTA. Systemic capsaicin increased plasma insulin levels after treatment,[35] which may account for the influences of capsaicin on the food intake and energy consumption and on the pathophysiological regulation of pancreatic endocrine function. Capsaicin caused a decrease in blood glucose levels when oral glucose tolerance tests (OGTT) were performed on dogs; this effect was ascribed to the insulin release mediated by capsaicin.[36] Kang et al.[37] re-

vealed that dietary capsaicin lowered fasting glucose, insulin, and leptin levels and markedly reduced the impairment of glucose tolerance in obese mice. The effects of capsaicin in adipose tissue and liver are related to its dual action on PPARα and TRPV1 expression/activation.[37]

A glucose loading test was evaluated in healthy human subjects by the simultaneous measurement of plasma level of glucose, C-peptide and glucagon without and with an oral application of capsaicin.[38] The plasma glucagon level increased after the glucose loading when capsaicin was administered. The plasma levels of insulin and C-peptide also increased after glucose loading but there were no significant differences between the results obtained without and with capsaicin administration. These results indicated that capsaicin increases the glucose absorption from the gastrointestinal tract and increases glucagon release (independently of the hormonal antagonist regulation by insulin released after glucose loading) during glucose loading tests carried out in human healthy subjects.[38]

These data establish the beneficial effects of capsaicin in diabetes mellitus (DM), as an agonist of TRPV1, however, some controversial data exist regarding TRPV1 from in vivo experiments. van de Wall et al.[39] reported that glucose-stimulated insulin secretion is attenuated in Wistar rats that were treated with capsaicin, even though their glucose levels did not differ. Karlsson and Ahren[40] discovered that sensory denervation results in increased glucose tolerance in mice, due in part to a potentiated insulin response to glucose. Razavi et al.[41] discovered that C57BL/6J mice with a TRPV1-null genotype have normal glucose regulation and are protected from insulin resistance. However, C57BL/6J mice are susceptible to diet-induced obesity and diabetes. Therefore, the results above indicated that studies using mice in a genetic background with normal glucose regulation should also be conducted to further study the physiological effects of TRPV1 deficiency. In addition, the role of TRPV1 in physiological

states is not fully understood.

Additionally, TRPV1^{+} fibers carrying a hypofunctional TRPV1 mutant play a specific role in the DM. The results from several experiments have indicated that the elimination of TRPV1^{+} fibers in Zucker diabetic fatty (ZDF) rats by capsaicin prevents the deterioration of glucose homeostasis by increasing insulin secretion and insulin responses.[42,43] Razavi et al.[41] discovered TRPV1^{+} fibers play a key role in type 1 diabetes. Ablation of nerves carrying this mutant TRPV1 by capsaicin prevents the immune-mediated destruction of islet beta cells. However, a congenic NOD strain with wild-type TRPV1 is also protected from diabetes, and the direct administration of SP into the pancreas transiently reverses hyperglycemia in diabetic NOD mice.[41] It is possible that the existence of a 'faulty neuronal circuit' caused by a mutant TRPV1 is responsible for the development of diabetes in genetically prone animals, regardless of the presence or absence of TRPV1. Thus, it may be worthwhile to explore the exact nature of the 'faulty neuronal circuit' mediated by TRPV1 channels in genetic and non-genetic diabetic models.[44]

Several findings suggest that capsaicin-sensitive nerves regulate glucose tolerance by improving insulin resistance through a mechanism that is independent of insulin release.[41,45] Because TRPV1^{+} fibers also innervate insulin target organs, such as skeletal muscle and liver, TRPV1 in these organs might also be involved in glucose tolerance. In addition, TRPV1 has recently been discovered in non-neuronal cells, including myocytes and hepatocytes.[46,47] However, its functional role has not yet been determined. Tissue-specific TRPV1-null mice may be useful for clarifying the *in vivo* effects of TRPV1 in various target tissues.

TRPV1 and lipid metabolism

Several studies have shown that TRPV1 affects lipid metabolism.[48,49] Our study demonstrated that TRPV1 cha-

nnels were expressed in 3T3-L1-preadipocytes.[11] Activation of TRPV1 channels by capsaicin resulted in reduced cellular triglyceride levels in 3T3-L1 preadipocytes during adipogenesis *in vitro*.[11] Manjunatha and Srinivasan[48] discovered dietary spice compound capsaicin reduced dietary high-fat-induced hypertriglyceridemia in rats on a high fat diet for 8 weeks. Tani et al.[49] revealed that after capsaicin administration, fatty acid synthase (FAS) activities were lower and hepatic triacylglycerol lipase (HTGL) activities tended to be higher than those fed a high-fat diet only. Lipoprotein lipase (LPL) activity in adipose tissue was higher in the capsaicin than the high-fat diet group. Even though consumed for a short period, capsaicin can be a potent antioxidant and aid in lowering low-density lipoprotein (LDL) in rats.[50] The level of serum triglyceride in rats was lower when capsaicin was present in the high-fat diet than when it was not. However, levels of serum cholesterol and pre-beta-lipoprotein were not affected by the supplementation of capsaicin. These results suggest that capsaicin lowers serum triglyceride concentrations in lard-fed rats.[51] These effects may be due to its lipophilic characteristics, as capsaicin seems to have an important role in lipid metabolism.[50]

Membrane lipid content can influence cellular TRPV1 channel distribution, localization, and function. Dietary intake of omega-3 fatty acids in humans is associated with a protective effect on cardiovascular health.[52] TRPV channels are an important class of omega-3 fatty acids targets.[53] It has been reported that omega-3 fatty acids differentially regulate TRPV1 in a phosphorylation-dependent manner.[53] Cholesterol depletion using methyl-β-cyclodextrin reduced TRPV1 protein levels in membrane fractions and TRPV1 mediated capsaicin and proton activated currents in adult rat dorsal root ganglion neurons.[54] These findings suggest that the dietary intake of lipids affects TRPV1 channels that are not directly involved in the regulation of circulating lipid levels.

TRPV1 and obesity

Obesity is a well-known risk factor for T2DM and CVD. Recently, increasing attention has been paid to the important roles of TRPV1 in obesity.

Studies show that CGRP from capsaicin-sensitive nerves plays a role in obesity. As discussed above, CGRP antagonizes insulin release and, in the long term, persistently high circulating CGRP levels cause insulin resistance and resultant obesity.[55] It is well documented that ablation of TRPV1-positive neurons by administration of a systemic agonist (capsaicin or resiniferatoxin, RTX) prevents the development of aging-associated insulin resistance.[56] Motter et al.[57] found that disruption of the TRPV1 gene protects against diet-induced obesity. Furthermore, they also demonstrated that preadipocytes are sensitive to CGRP, thus revealing a potential neurogenic mechanism through which TRPV1-expressing neurons may regulate adipocyte function. Circulating CGRP levels increase during aging, and it was speculated that this phenomenon might play a crucial role in the development of insulin resistance and resulting obesity. Because TRPV1-expressing nerves are a major source of CGRP, TRPV1 antagonists might help prevent aging-associated insulin resistance and obesity. However, once somatic small fiber neuropathy has developed in obese patients, it could be too late for TRPV1 antagonist therapy.[56] Obese patients show markedly reduced capsaicin-evoked flare responses in their skin that could be interpreted to imply downregulated TRPV1 expression and/or loss of TRPV1-positive nerve fibers. It is unclear whether or not the reduction of TRPV1 in obese subjects is due to down-regulation in response to high levels of CGRP.[58]

Studies of both animals and humans implicated capsaicin is associated with energy expenditure and obesity prevention as a TRPV1 agonist. Several studies have shown that acute oral capsaicin administration promotes oxygen consumption and fat utilization in rodents.[59,60] Rodents fed a diet containing capsaicin, a dose equivalent to that ingested by rural Thai people, showed no change in caloric intake but a significant reduction in the visceral fat weight.[59,61] Leung[62] discovered that the stimulation of intestinal mucosal afferent nerves with capsaicin produces an increase in gut blood flow, which is attenuated by a TRPV1 antagonist. This finding may partially explain why capsaicin intake reduces visceral fat accumulation but has little effect on body weight. However, the effects of oral capsaicin on blood distribution require confirmation *in vivo*. Epidemiological data have revealed that the consumption of foods containing capsaicin is associated with a lower prevalence of obesity.[9] Chili pepper consumption for 4 weeks attenuated postprandial glucose levels and increased energy expenditure in middle-aged subjects.[8] A single dose of capsaicin enhances fat oxidation during aerobic exercise in healthy humans.[7] Two studies involving subjects with high body mass indexes showed that intake of capsinoids both enhanced fat oxidation and significantly reduced abdominal adiposity.[63] Although capsaicin has been shown to promote fat oxidation, its effects on the reduction of body weight are complex.

The underlying mechanisms and roles of the capsaicin receptor TRPV1 have been investigated. Experiments have shown that activation of TRPV1 can affect preadipocyte differentiation, obesity-induced chronic inflammatory responses, fat distribution via afferent autonomic nerves and appetite regulation.[44,64]

We demonstrated TRPV1 channels are present in 3T3-L1-preadipocytes and visceral adipose tissue from mice and humans.[11] Capsaicin dose-dependently induced calcium influx and prevented adipogenesis in 3T3-L1-preadipocytes, through the inhibition of peroxisome proliferator-activated receptor-γ (PPAR-γ) expression in preadipocytes. TRPV1 expression decreased in visceral adipose tissue from obese humans and db/db mice. Chronic

dietary capsaicin consumption prevented high-fat diet-induced obesity in WT mice, but not in TRPV1-null mice. This study indicates that capsaicin may prevent adipogenesis and obesity through a direct action on TRPV1 channels in adipocytes.[11] Kanga et al.[37] showed that capsaicin could suppress obesity-induced inflammation through nuclear factor (NF)-κB inactivation and/or PPAR-γ activation in the adipose tissues of obese mice. Hypothalamic AMP-activated protein kinase (AMPK) has been shown to integrate the nutritional and hormonal signals that modulate feeding behavior and energy expenditure. Hwang et al.[65] reported that capsaicin could inhibit adipogenesis and stimulate reactive oxidative species (ROS) release, which rapidly activates AMPK in 3T3-L1 cells. Two weeks of treatment with capsiate, a non-pungent capsaicin analogue, have been shown to increase metabolic rate and fat oxidation, as well as increase uncoupling protein (UCP) levels in adipose tissue.[66] In summary, these results suggest that

capsaicin and its analogue have complex effects on the cellular processes related to obesity. The role of TRPV1 in these processes deserves further evaluation.

Summary

Emerging data indicate that TRPV1 plays an important role in cardiovascular and metabolic disease. As we reviewed before, the consumption of a capsaicin-rich diet may decrease cardiometabolic risk (Fig. 2). Therefore, TRPV1 could be considered as a new therapeutic target for the management of cardiometabolic diseases. However, some questions remain to be elucidated in the future. First, the design and development of more specific agonists and antagonists for TRPV1 channels will promote research in this field. Next, interactions between TRPV1 and other TRP channels need to be studied in-depth.
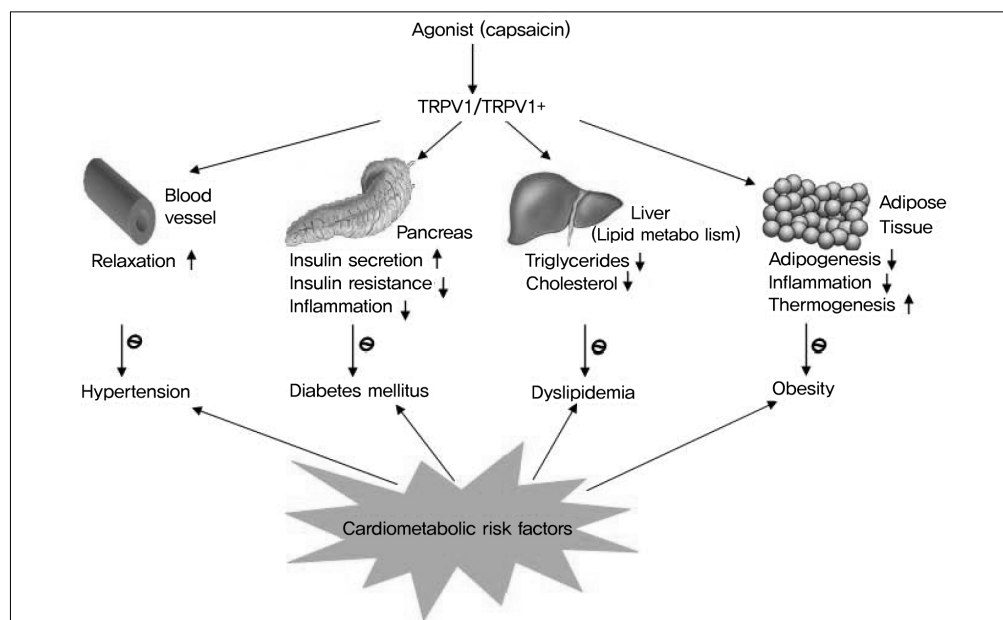

Fig. 2. Transient receptor potential vanilloid type-1 channel (TRPV1) is widely expressed in the cardiometabolic system such as in pancreas, blood vessels, adipose tissue and liver. Activation of TRPV1 causes the relaxation of arteries leading to a decrease in blood pressure; increases the secretion of insulin from islet β cells and lowers blood glucose; improves insulin resistance; reduces inflammation, triglycerides, cholesterol, and adipogenesis; increases thermogenesis; and prevents obesity, implying that activation of TRPV1 will decrease cardiometabolic risk.

References

1. Wyne KL. Preventing cardiovascular disease and diabetes: a call to action from the ADA and AHA. J Cardiometab Syndr. 2006;1:220-1.

2. Eckel RH, Kahn R, Robertson RM, Rizza RA. Preventing cardiovascular disease and diabetes: a call to action from the American Diabetes Association and the American Heart Association. Circulation. 2006;113:2943-6.

3. Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, Stein JH, et al. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. Diabetes Care. 2008; 31:811-22.

4. Plutzky J. Preventing type 2 diabetes and cardiovascular disease in metabolic syndrome: the role of PPARalpha. Diab Vasc Dis Res. 2007;4 Suppl 3:S12-4.

5. American Heart Association Nutrition Committee, Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. Circulation. 2006;114:82-96.

6. Bibbins-Domingo K, Chertow GM, Coxson PG, Moran A, Lightwood JM, Pletcher MJ, et al. Projected effect of dietary salt reductions on future cardiovascular disease. N Engl J Med. 2010;362:590-9.

7. Shin KO, Moritani T. Alterations of autonomic nervous activity and energy metabolism by capsaicin ingestion during aerobic exercise in healthy men. J Nutr Sci Vitaminol (Tokyo). 2007;53:124-32.

8. Ahuja KD, Robertson IK, Geraghty DP, Ball MJ. Effects of chili consumption on postprandial glucose, insulin, and energy metabolism. Am J Clin Nutr. 2006;84:63-9.

9. Wahlqvist ML, Wattanapenpaiboon N. Hot foods-unexpected help with energy balance? Lancet. 2001;358: 348-9.

10. Yang D, Luo Z, Ma S, Wong WT, Ma L, Zhong J, et al. Activation of TRPV1 by dietary capsaicin improves endothelium-dependent vasorelaxation and prevents hypertension. Cell Metab. 2010;12:130-41.

11. Zhang LL, Yan Liu D, Ma LQ, Luo ZD, Cao TB, Zhong J, et al. Activation of transient receptor potential vanilloid type-1 channel prevents adipogenesis and obesity. Circ Res. 2007;100:1063-70.

12. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature. 1997;389: 816-24.

13. Nagy I, Santha P, Jancso G, Urban L. The role of the vanilloid (capsaicin) receptor (TRPV1) in physiology and pathology. Eur J Pharmacol. 2004;500:351-69.

14. Sessa WC. A new way to lower blood pressure: pass the chili peppers please! Cell Metab. 2010;12:109-10.

15. Gunthorpe MJ, Szallasi A. Peripheral TRPV1 receptors as targets for drug development: new molecules and mechanisms. Curr Pharm Des. 2008;14:32-41.

16. Luo D, Zhang YW, Peng WJ, Peng J, Chen QQ, Li D, et al. Transient receptor potential vanilloid 1-mediated expression and secretion of endothelial cell-derived calcitonin gene-related peptide. Regul Pept. 2008;150:66-72.

17. Sudhahar V, Shaw S, Imig JD. Mechanisms involved in oleamide-induced vasorelaxation in rat mesenteric resistance arteries. Eur J Pharmacol. 2009;607:143-50.

18. Franco-Cereceda A. Resiniferatoxin-, capsaicin- and CGRP-evoked porcine coronary vasodilatation is independent of EDRF mechanisms but antagonized by CGRP(8-37). Acta Physiol Scand. 1991;143:331-7.

19. Deng PY, Li YJ. Calcitonin gene-related peptide and hypertension. Peptides. 2005;26:1676-85.

20. Deng PY, Ye F, Cai WJ, Deng HW, Li YJ. Role of calcitonin gene-related peptide in the phenol-induced neurogenic hypertension in rats. Regul Pept. 2004;119:155-61.

21. White CB, Roberts AM, Joshua IG. Arteriolar dilation mediated by capsaicin and calcitonin gene-related peptide in rats. Am J Physiol. 1993;265:H1411-5.

22. Li J, Wang DH. High-salt-induced increase in blood pressure: role of capsaicin-sensitive sensory nerves. J Hypertens. 2003;21:577-82.

23. Poblete IM, Orliac ML, Briones R, Adler-Graschinsky E, Huidobro-Toro JP. Anandamide elicits an acute release of nitric oxide through endothelial TRPV1 receptor activation in the rat arterial mesenteric bed. J Physiol. 2005; 568:539-51.

24. Bratz IN, Dick GM, Tune JD, Edwards JM, Neeb ZP, Dincer UD, et al. Impaired capsaicin-induced relaxation of coronary arteries in a porcine model of the metabolic syndrome. Am J Physiol Heart Circ Physiol. 2008;294: H2489-96.

25. Hao X, Chen J, Luo Z, He H, Yu H, Ma L, et al. TRPV1 activation prevents high-salt diet-induced nocturnal hypertension in mice. Pflugers Arch. 2011;461:345-53.

26. Wang DH. The vanilloid receptor and hypertension. Acta Pharmacol Sin. 2005;26:286-94.

27. Wang Y, Kaminski NE, Wang DH. Endocannabinoid regulates blood pressure via activation of the transient receptor potential vanilloid type 1 in Wistar rats fed a high-salt diet. J Pharmacol Exp Ther. 2007;321:763-9.

28. Qin XP, Zeng SY, Li D, Chen QQ, Luo D, Zhang Z, et al. Calcitonin gene-related Peptide-mediated depressor effect and inhibiting vascular hypertrophy of rutaecarpine in renovascular hypertensive rats. J Cardiovasc Pharmacol. 2007;50:654-9.

29. Wang Y, Babankova D, Huang J, Swain GM, Wang DH. Deletion of transient receptor potential vanilloid type 1 receptors exaggerates renal damage in deoxycorticosterone acetate-salt hypertension. Hypertension. 2008;52:264-70.

30. Sexton A, McDonald M, Cayla C, Thiemermann C, Ahluwalia A. 12-Lipoxygenase-derived eicosanoids protect against myocardial ischemia/reperfusion injury via activation of neuronal TRPV1. FASEB J. 2007;21:2695-703.

31. Wang L, Wang DH. TRPV1 gene knockout impairs postischemic recovery in isolated perfused heart in mice. Circulation. 2005;112:3617-23.

32. Li YJ, Xiao ZS, Peng CF, Deng HW. Calcitonin gene-related peptide-induced preconditioning protects against ischemia-reperfusion injury in isolated rat hearts. Eur J Pharmacol. 1996;311:163-7.

33. Huang W, Rubinstein J, Prieto AR, Thang LV, Wang DH. Transient receptor potential vanilloid gene deletion exacerbates inflmation and atypical cardiac remodeling after myocardial infarction. Hypertension. 2009;53:243-50.

34. Zhong B, Wang DH. TRPV1 gene knockout impairs preconditioning protection against myocardial injury in isolated perfused hearts in mice. Am J Physiol Heart Circ Physiol. 2007;293:H1791-8.

35. Akiba Y, Kato S, Katsube K, Nakamura M, Takeuchi K, Ishii H, et al. Transient receptor potential vanilloid subfamily 1 expressed in pancreatic islet beta cells modulates insulin secretion in rats. Biochem Biophys Res Commun. 2004;321:219-25.

36. Tolan I, Ragoobirsingh D, Morrison EY. The effect of capsaicin on blood glucose, plasma insulin levels and insulin binding in dog models. Phytother Res. 2001;15:391-4.

37. Kang JH, Kim CS, Han IS, Kawada T, Yu R. Capsaicin, a spicy component of hot peppers, modulates adipokine gene expression and protein release from obese-mouse adipose tissues and isolated adipocytes, and suppresses the inflammatory responses of adipose tissue macrophages. FEBS Lett. 2007;581:4389-96.

38. Domotor A, Szolcsanyi J, Mozsik G. Capsaicin and glucose absorption and utilization in healthy human subjects. Eur J Pharmacol. 2006;534:280-3.

39. van de Wall EH, Gram DX, Strubbe JH, Scheurink AJ, Koolhaas JM. Ablation of capsaicin-sensitive afferent nerves affects insulin response during an intravenous glucose tolerance test. Life Sci. 2005;77:1283-92.

40. Karlsson S, Ahren B. Capsaicin-induced sensory denervation increases glucose elimination in rodents. Diabetologia. 1999;42:260-1.

41. Razavi R, Chan Y, Afifiyan FN, Liu XJ, Wan X, Yantha J, et al. TRPV1+ sensory neurons control beta cell stress and islet inflammation in autoimmune diabetes. Cell. 2006; 127:1123-35.

42. Gram DX, Ahren B, Nagy I, Olsen UB, Brand CL, Sundler F, et al. Capsaicin-sensitive sensory fibers in the islets of Langerhans contribute to defective insulin secretion in Zucker diabetic rat, an animal model for some aspects of human type 2 diabetes. Eur J Neurosci. 2007;25:213-23.

43. Gram DX, Hansen AJ, Deacon CF, Brand CL, Ribel U, Wilken M, et al. Sensory nerve desensitization by resiniferatoxin improves glucose tolerance and increases insulin secretion in Zucker Diabetic Fatty rats and is associated with reduced plasma activity of dipeptidyl peptidase IV. Eur J Pharmacol. 2005;509:211-7.

44. Suri A, Szallasi A. The emerging role of TRPV1 in diabetes and obesity. Trends Pharmacol Sci. 2008;29:29-36.

45. Guillot E, Coste A, Angel I. Involvement of capsaicin-sensitive nerves in the regulation of glucose tolerance in diabetic rats. Life Sci. 1996;59:969-77.

46. Xin H, Tanaka H, Yamaguchi M, Takemori S, Nakamura A, Kohama K. Vanilloid receptor expressed in the sarcoplasmic reticulum of rat skeletal muscle. Biochem Biophys Res Commun. 2005;332:756-62.

47. Castro J, Aromataris EC, Rychkov GY, Barritt GJ. A small component of the endoplasmic reticulum is required for

store-operated Ca2+ channel activation in liver cells: evidence from studies using TRPV1 and taurodeoxycholic acid. Biochem J. 2009;418:553-66.

48. Manjunatha H, Srinivasan K. Hypolipidemic and antioxidant effects of curcumin and capsaicin in high-fat-fed rats. Can J Physiol Pharmacol. 2007;85:588-96.

49. Tani Y, Fujioka T, Sumioka M, Furuichi Y, Hamada H, Watanabe T. Effects of capsinoid on serum and liver lipids in hyperlipidemic rats. J Nutr Sci Vitaminol (Tokyo). 2004; 50:351-5.

50. Lee CY, Kim M, Yoon SW, Lee CH. Short-term control of capsaicin on blood and oxidative stress of rats in vivo. Phytother Res. 2003;17:454-8.

51. Kawada T, Hagihara K, Iwai K. Effects of capsaicin on lipid metabolism in rats fed a high fat diet. J Nutr. 1986;116: 1272-8.

52. Kahn-Kirby AH, Dantzker JL, Apicella AJ, Schafer WR, Browse J, Bargmann CI, et al. Specific polyunsaturated fatty acids drive TRPV-dependent sensory signaling in vivo. Cell. 2004;119:889-900.

53. Matta JA, Miyares RL, Ahern GP. TRPV1 is a novel target for omega-3 polyunsaturated fatty acids. J Physiol. 2007; 578:397-411.

54. Liu M, Huang W, Wu D, Priestley JV. TRPV1, but not P2X, requires cholesterol for its function and membrane expression in rat nociceptors. Eur J Neurosci. 2006;24:1-6.

55. Melnyk A, Himms-Hagen J. Resistance to aging-associated obesity in capsaicin-desensitized rats one year after treatment. Obes Res. 1995;3:337-44.

56. Herman RM, Brower JB, Stoddard DG, Casano AR, Targovnik JH, Herman JH, et al. Prevalence of somatic small fiber neuropathy in obesity. Int J Obes (Lond). 2007; 31:226-35.

57. Motter AL, Ahern GP. TRPV1-null mice are protected from diet-induced obesity. FEBS Lett. 2008;582:2257-62.

58. Pare M, Albrecht PJ, Noto CJ, Bodkin NL, Pittenger GL, Schreyer DJ, et al. Differential hypertrophy and atrophy among all types of cutaneous innervation in the glabrous skin of the monkey hand during aging and naturally occurring type 2 diabetes. J Comp Neurol. 2007;501:543-67.

59. Kawada T, Watanabe T, Takaishi T, Tanaka T, Iwai K. Capsaicin-induced beta-adrenergic action on energy metabolism in rats: influence of capsaicin on oxygen consumption, the respiratory quotient, and substrate utilization. Proc Soc Exp Biol Med. 1986;183:250-6.

60. Kim KM, Kawada T, Ishihara K, Inoue K, Fushiki T. Increase in swimming endurance capacity of mice by capsaicin-induced adrenal catecholamine secretion. Biosci Biotechnol Biochem. 1997;61:1718-23.

61. Ohnuki K, Haramizu S, Oki K, Watanabe T, Yazawa S, Fushiki T. Administration of capsiate, a non-pungent capsaicin analog, promotes energy metabolism and suppresses body fat accumulation in mice. Biosci Biotechnol Biochem. 2001;65:2735-40.

62. Leung FW. Capsaicin-sensitive intestinal mucosal afferent mechanism and body fat distribution. Life Sci. 2008;83: 1-5.

63. Inoue N, Matsunaga Y, Satoh H, Takahashi M. Enhanced energy expenditure and fat oxidation in humans with high BMI scores by the ingestion of novel and non-pungent capsaicin analogues (capsinoids). Biosci Biotechnol Biochem. 2007;71:380-9.

64. Wang X, Miyares RL, Ahern GP. Oleoylethanolamide excites vagal sensory neurones, induces visceral pain and reduces short-term food intake in mice via capsaicin receptor TRPV1. J Physiol. 2005;564:541-7.

65. Hwang JT, Park IJ, Shin JI, Lee YK, Lee SK, Baik HW, et al. Genistein, EGCG, and capsaicin inhibit adipocyte differentiation process via activating AMP-activated protein kinase. Biochem Biophys Res Commun. 2005;338:694-9.

66. Masuda Y, Haramizu S, Oki K, Ohnuki K, Watanabe T, Yazawa S, et al. Upregulation of uncoupling proteins by oral administration of capsiate, a nonpungent capsaicin analog. J Appl Physiol. 2003;95:2408-15.