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Capsaicin may have important potential for promoting vascular and metabolic health

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ABSTRACT

Capsaicin, the phytochemical responsible for the spiciness of peppers, has the potential to modulate metabolism via activation of transient receptor potential vanilloid 1 (TRPV1) receptors, which are found not only on nociceptive sensory neurons, but also in a range of other tissues. TRPV1 activation induces calcium influx, and in certain tissues this is associated with increased activation or expression of key proteins such as endothelial nitric oxide synthase (eNOS), uncoupling protein 2 (UCP2), KLF2, PPARdelta, PPARgamma, and LXRα. The calcium influx triggered by TRPV1 activation in endothelial cells mimics the impact of shear stress in this regard, activating and increasing the expression of eNOS—but also increasing expression of cox-2, thrombomodulin, and nrf2-responsive antioxidant enzymes, while decreasing expression of proinflammatory proteins. Hence, dietary capsaicin has favourably impacted endothelium-dependent vasodilation in rodents. TRPV1-mediated induction of LXRα in foam cells promotes cholesterol export, antagonising plaque formation. Capsaicin-mediated activation of TRPV1-expressing neurons in the gastrointestinal tract promotes sympathetically mediated stimulation of brown fat, raising metabolic rate. The increased expression of UCP2 induced by TRPV1 activation exerts a protective antioxidant effect on the liver in non-alcoholic fatty liver disease, and on vascular endothelium in the context of hyperglycaemia. In rodent studies, capsaicin-rich diets have shown favourable effects on atherosclerosis, metabolic syndrome, diabetes, obesity, non-alcoholic fatty liver, cardiac hypertrophy, hypertension and stroke risk. Clinically, ingestion of capsaicin—or its less stable non-pungent analogue capsiate—has been shown to boost metabolic rate modestly. Topical application of capsaicin via patch was found to increase exercise time to ischaemic threshold in patients with angina. Further clinical studies with capsaicin administered in food, capsules, or via patch, are needed to establish protocols that are tolerable for most patients, and to evaluate the potential of capsaicin for promoting vascular and metabolic health.

CAPSAICIN STIMULATES THE TRPV1 RECEPTOR

Transient receptor potential vanilloid 1 (TRPV1) is a membrane receptor that, when activated, acts as a non-specific cation channel, allowing influx of calcium. Endogenous activators of TRPV1 include heat, low pH, and certain lipid metabolites; the best known exogenous activator is the phytochemical capsaicin, responsible for the spiciness in peppers.[1–3] Inasmuch as nanomolar concentrations of capsaicin can activate this receptor (EC_{50}=99 nM[4]), and capsaicin is efficiently absorbed,[5] a sufficiently high oral intake of capsaicin can induce systemic activation of TRPV1.

Few studies have evaluated the clinical pharmacokinetics of orally administered capsaicin.[6] After acute ingestion of 5 g of a capsaicin-rich hot pepper extract, a peak serum capsaicin level of 8.2 nM was observed after 45 min; an hour later, capsaicin was no longer detectible, presumably owing to rapid hepatic metabolism.[7] In mice given a bolus dose of 10 mg/kg capsaicin—far higher than humans could be expected to use—the peak serum concentration was about 3 μM; after 8 h, capsaicin was undetectable in serum. It is therefore reasonable to expect that clinically tolerable intakes of capsaicin will achieve serum concentrations in the nanomolar range. Although capsaicin can inhibit certain voltage-sensitive calcium channels with an EC_{50} of 5 μM or higher,[8 9] it does not appear likely that this effect would be germane with feasible oral intakes of capsaicin in humans.

TRPV1 is expressed by many nociceptive sensory neurons, and its activation triggers pain sensations. However, the massive neuronal calcium influx triggered by topical exposure to sufficient concentrations of capsaicin is potentially cytotoxic, and triggers a reflex down-regulation of TRPV1 activity.[10] Hence, these neurons become less responsive to endogenous agonists for TRPV1, resulting in analgesia.[11 12] Capsaicin skin patches are currently employed clinically for local pain control.[13]

TRPV1 is also expressed by vascular endothelial cells, hepatocytes, adipocytes, smooth

muscle cells, fibroblasts, various epithelia, T cells, mast cells, and by neurons and astrocytes in the brain and spinal column.[14] Hence, TRPV1 has the potential to modulate the function of these cells by boosting their intracellular-free calcium levels (Ca_i). At present, there does not appear to be any evidence that the desensitisation phenomenon evoked by capsaicin in sensory neurons is pertinent to these other tissues; no down-regulation of TRPV1 expression or function was noted in the vasculature of newborn rats that had been injected with potent doses of capsaicin for 5 days.[15]

CAPSAICIN CAN INCREASE EXPRESSION AND ACTIVATION OF ENOS

The impact of TRPV1 activation on vascular endothelium is of particular interest, since an increase in Ca_i is a key mediator of the protective impact of pulsatile shear stress—and of aerobic exercise—on endothelial function. This increase in Ca_i acts rapidly to stimulate endothelial nitric oxide synthase (eNOS) activity via binding of the Ca^{2+}/calmodulin complex; in addition, Ca_i-mediated activation of AMPK and Sirt1 stimulates eNOS activity by modifying its phosphorylation and acetylation status.[16 17] In the longer term, expression of eNOS increases as well. Increased Ca_i acts to boost the expression and activity of the endothelium-specific transcription factor KLF2 via a complex chain of events involving activation of Ca2+/calmodulin-dependent kinase kinase-β and downstream phosphorylations of AMPK, ERK2, HDAC5, and the transcription factor MEF2.[18 19] KLF2, in turn, promotes transcription of the eNOS, thrombomodulin, and Nrf2-responsive antioxidant enzymes, and works indirectly to suppress transcription of various proinflammatory proteins.[20–24]

As might be expected, treatment of endothelial cells with capsaicin leads to increased expression and activation of eNOS.[25 26] Consistent with this, in wild-type, but not TRPV1-knockout mice, dietary capsaicin enhances endothelium-dependent vasodilation.[27] In spontaneously hypertensive stroke-prone rats, dietary capsaicin increases activation and expression of eNOS in the cerebrovasculature, an effect associated with a reduction of arteriolar hypertrophy, a delay in stroke occurrence, and an increase in mean survival time.[28] In atherosclerosis-prone ApoE knockout mice, dietary capsaicin slows atherogenesis,[26 29] an effect which may reflect improved endothelial function, but also a favourable impact of TRPV1 activation on foam cells, increasing the expression of membrane transporters that mediate cholesterol efflux; this latter effect is contingent on increased expression of the transcription factor LXRα.[30] The potential clinical relevance of these findings is demonstrated by a controlled crossover study in which patients with stable coronary disease and angina were treated with capsaicin skin patches (typically employed for control of lower back pain) or placebo patches. During exercise testing, average time until ischaemic threshold (1 mm ST segment depression) was significantly higher during capsaicin administration (424 s vs 372 s, p=0.027).[31] Notably, serum NO levels (assessed by measuring its stable metabolites nitrate and nitrite) were found to be significantly higher when the patients were using the capsaicin patches, suggesting that increased NO production within the coronary tree may have been responsible for the improved exercise tolerance associated with capsaicin.

Capsaicin feeding has shown an antihypertensive effect in rats genetically prone to this disorder, and this compound also blunts the nocturnal rise in blood pressure or development of hypertension in mice fed a high salt diet.[27 32 33] Conceivably, improved NO function may underlie these effects. Capsaicin dilates the coronary arteries of pigs ex vivo, an effect that is half-maximal at 116 nM; this effect is blocked by endothelial denudation and inhibitors of eNOS, and is less notable with coronaries from pigs experiencing metabolic syndrome, which disrupts eNOS function via oxidative stress.[34] Release of CGRP from perivascular sensory neurons may also contribute to the vasodilatory impact of capsaicin.[35] Paradoxically, the direct impact of capsaicin on vascular smooth muscle is to provoke constriction, owing to increased calcium influx.[36] Hence, the net impact of capsaicin on vascular tone and blood pressure may reflect complex interactions and countervailing effects. Several case histories of acute hypertensive crisis provoked by very high intakes of chilli peppers have appeared; down-regulated function of CGRP-producing neurons owing to acute high capsaicin exposure has been suggested as an explanation for this effect.[37 38] On the other hand, a more moderate capsaicin exposure associated with the use of capsaicin patches—sufficient to alleviate angina pain—did not alter plasma levels of CGRP, but plasma levels of NO metabolites increased.[31] Whether and how moderate, clinically tolerable dosing with capsaicin would influence human hypertension has not yet been assessed.

The antihypertensive effect of dietary capsaicin in salt-fed rats may reflect, in part, an inhibitory effect on renal sodium retention. In the kidney, cortical collecting duct epithelium expresses TPRV1, and its activation decreases the function and expression of epithelial sodium channels in these cells, resulting in increased urinary sodium loss.[33]

CAPSAICIN BOOSTS UCP2 EXPRESSION IN CERTAIN TISSUES

TRPV1 activation has also been shown to increase expression of uncoupling protein 2 (UCP2) in endothelial cells, hepatocytes and cardiac tissue.[39–41] In the heart, this effect may be downstream from increased expression of PPARdelta, a factor which opposes cardiac hypertrophy and fibrosis.[41 42] Hence, dietary capsaicin was found to oppose the cardiac hypertrophy induced by a high salt diet in mice—an effect not seen in TRPV1

knockout mice.[41] With respect to UCP2, this functions as a mitochondrial uncoupling protein when mitochondrial substrate oxidation is high and superoxide generation is elevated; by diminishing the proton gradient across the mitochondrial inner membrane, UCP2 relieves the resistance to electron flow down the respiratory chain and hence decreases the rate at which electrons are shunted to superoxide generation at complexes I and III.[43–45]

UCP2 can be of particular value when cells that are constitutively permeable to glucose—such as vascular endothelium—are subjected to hyperglycaemia. Under these circumstances, elevated glucose oxidation in the Krebs cycle tends to boost mitochondrial superoxide generation, an effect opposed by UCP2.[46–48] In diabetic mice, capsaicin administration was shown to alleviate vascular oxidative stress and improve endothelium-dependent vasodilation—a phenomenon not seen in UCP2 knockout mice rendered diabetic.[39] In men with diabetes, a polymorphism in the UCP2 promoter (-866G>A), linked to increased expression of UCP2 in some studies, was found to be associated with significantly lower risk for developing coronary disease[49]—consistent with a protective impact of UCP2 expression on cardiovascular risk in diabetics.

Hepatocyte expression of UCP2 can be protective in the context of non-alcoholic fatty liver disease. Under these circumstances, increased mitochondrial oxidation of fatty acids contributes to the oxidative stress that plays a mediating role in this syndrome. The uncoupling activity of UCP2 decreases this generation of superoxide, and by boosting the rate at which mitochondria can metabolise fatty acids, helps to mitigate the surplus of fatty acids within hepatocytes.[50 51] Indeed, capsaicin-rich diets have been found to alleviate non-alcoholic fatty liver disease in mouse models of this disorder.[39 52] TRPV1-mediated induction of PPARdelta likely plays a role in this effect, and may be upstream from UCP2 induction.[52] Capsaicin-mediated induction of UCP2 in hepatocytes may have potential as an adjuvant to weight control strategies which attempt to optimise hunger control, selective fat oxidation, and thermogenesis by improving the efficiency of hepatic fatty acid oxidation.[53]

CAPSAICIN EFFICACY IN METABOLIC SYNDROME

In obese mice, capsaicin injections exert an anti-inflammatory effect on adipose tissue, suppressing production of IL-6, TNF-α, MCP-1, and cox-2, while boosting that of adiponectin, and decreasing macrophage infiltration.[54] The authors of this study speculate that enhanced activity of PPARgamma might account for these effects, although they do not present evidence to support this contention. A subsequent study showed that dietary capsaicin had a beneficial metabolic impact on genetically diabetic KKAy mice—reducing plasma levels of glucose, insulin and triglycerides, boosting those of adiponectin, and exerting the same anti-inflammatory effects on adipose tissue as reported in the previous study.[55] And more recent studies with topically applied or dietary capsaicin in fat-fed mice did indeed confirm that adipose expression of PPARgamma was increased in the treated mice, whereas gain in weight and visceral fat mass were blunted.[56 57] One of these studies reported that capsaicin treatment also boosted visceral adipose expression of hormone-sensitive lipase and of connexin-43; the latter is required for gap junctional communications between adipocytes that are required for efficient lipolysis.[57] This study also demonstrated that exposure of mesenteric adipose tissue from obese humans to capsaicin, likewise increased expression of these proteins.[57]

The beneficial effects of capsaicin on metabolic syndrome in mice may be mediated in part by increased secretion of glucagon-like peptide-1 (GLP-1). Indeed, gastric administration of capsaicin has been shown to evoke increased secretion of GLP-1 by the gastrointestinal (GI) tract, and to raise plasma levels of this factor.[58] This effect is absent in TRPV1 knockout mice. Increased calcium influx into intestinal L cells may mediate this impact on GLP-1 secretion.

How activation of the TRPV1 receptor manages to increase the expression of various regulatory factors—UCP2, PPARalpha and PPARdelta, LXRα—remains obscure; calcium influx per se seems unlikely to mediate all these effects. Perhaps TRPV1 has a distinctive microenvironment reflecting binding affinities to other proteins, such that influxing calcium tends to preferentially activate certain calcium-binding proteins in this microenvironment. It is also conceivable that some of TRPV1's signalling effects are independent of calcium influx.

THERMOGENIC AND APPETITE CONTROL EFFECTS OF CAPSAICIN AND CAPSIATE

Another intriguing TRPV1-dependent effect of capsaicin ingestion is activation of brown adipose tissue. Activation of TRPV1-expressing neurons in the digestive tract sends a signal to the brain via the vagal nerve; this in turn evokes an activation of sympathetic neurons that is selective for brown fat—that is, the heart rate is not impacted.[59 60] Many clinical trials have evaluated the impact of capsaicin ingestion on metabolic rate, respiratory quotient and appetite; these conclude that capsaicin can modestly enhance energy expenditure, while boosting fat oxidation (lower RQ) and diminishing appetite—effects conducive to weight control.[61 62]

Similar effects are seen with a non-spicy analogue of capsaicin, capsiate, which owing to lower stability does not induce pain in the oral cavity and appears to have limited systemic availability.[59 60 63–65] Capsiate is found in certain sweet peppers; it is very similar in structure to capsaicin, and can activate TRPV1, with an affinity about one-third that of capsaicin (EC50=290 nM).[4] Whereas capsaicin contains an amide linkage that is relatively

stable, capsiate contains an ester that is readily cleaved; when administered orally, intact capsiate fails to reach oral TPRV1-expressing neurons, but does manage to stimulate such neurons lower in the GI tract. No intact capsiate appears in the portal blood after oral administration, but its hydrolysis products are detectible, implying that capsiate is hydrolysed during the process of absorption.[65] Hence, the effects of capsiate attributable to TPRV1 agonism appear to be mediated by stimulation of GI sensory neurons.

Both capsaicin and capsiate may have modest utility as adjuvants to weight control programmes. Supplementation with capsiate (9 mg daily) for 12 weeks in a double-blind study was shown to decrease abdominal fat mass relative to placebo, albeit to a modest extent.[66] (Over the 12 weeks, the capsiate group, on average, lost 0.4 kg of weight and 1 cm of waist girth beyond that achieved with placebo—not an effect of much practical importance unless it persists and increases over time.) Not surprisingly, the effects of capsaicin or capsiate on thermogenesis are most notable in humans bearing detectible amounts of brown fat;[63] however, there is some evidence that prolonged ingestion of these agents may lead to recruitment of brown fat in humans.[67] These effects on thermogenesis are modest in magnitude; there do not appear to be any reports of clinically significant hyperthermia with ingestion of capsaicin or capsiate.

Some studies have also evaluated the impact of oral capsaicin or capsiate on appetite and subsequent food consumption in various contexts. The findings of these studies have been inconsistent, though an overview of these studies by Ludy *et al*[61] concludes that, on balance, consumption of these agents tends to decrease orexigenic sensations. In positive studies, capsaicin-treated subjects reported less desire to consume fatty foods, sweet foods, salty foods and food overall, and achieved greater satiety after meals. Also, calorie consumption during subsequent meals was sometimes reported to drop after capsaicin consumption. The fact that capsiate blunted appetite in some studies suggests that these effects are mediated by TRPV1-expressing GI neurons. Arguably, capsaicin in the GI tract triggers a vagal signal to appetite-regulatory centres in the brain; however, increased secretion of GLP-1 may also play a role in capsaicin's impact on appetite.

IMPACT ON GASTRIC PATHOLOGY

Ironically, many laypeople are under the impression that spicy foods can cause ulcers; to the contrary, there is evidence that capsaicin tends to prevent and accelerate healing of gastric ulcers.[68–70] This phenomenon reflects capsaicin's ability to inhibit gastric acid secretion, boost secretion of alkali and mucous, and stimulate gastric blood flow. A clinical study found that the gastric tissue damage and microbleeding induced acutely by indomethacin or ethanol ingestion was blunted if capsaicin was administered concurrently.[69] These findings have prompted the suggestion that capsaicin could be used as a protective adjuvant to non-steroidal anti-inflammatory drug therapy.[69 70] Limited epidemiology suggests that gastric ulcers may be less common in ethnic groups that prefer spicy foods.[68]

With respect to risk of gastric cancer, the epidemiology on spicy foods is rather perplexing. A recent meta-analysis of pertinent studies in Korea and Mexico, where heavy consumption of spicy foods is common, concludes that moderate daily intakes of capsaicin (less than 30 mg daily) are associated with a significant decrease in gastric cancer risk (OR=0.55, p=0.003) relative to non-consumption—perhaps reflecting the gastroprotective effects of capsaicin—whereas, heavy daily consumption is associated with a notable increase in risk (OR=1.94, p=0.0004).[71] Bley *et al*[72] suggest that the increase in risk associated with heavy consumption of spicy traditional foods might reflect mutagens present in these foods, rather than an effect of capsaicin per se. Aflatoxins, pesticides and nitrosamines or their precursors have been detected in chillies sold for human consumption.[72] The traditional Korean dish kimchi, a salty pickled cabbage usually fermented with red pepper and linked to increased risk of gastric cancer, is typically high in nitrate and contains N-nitroso compounds with mutagenic potential; the high salt content of this food may act as gastric co-carcinogen.[73–76] Studies with high-purity capsaicin indicate that it is not genotoxic; in animal studies, capsaicin lacks carcinogenicity, and opposes the carcinogenicity of certain mutagens.[72] Further clarification of this situation will be desirable if in the future people are encouraged to consume more capsaicin for potential health benefits.

DOSAGE CONSIDERATIONS

In rodents, large metabolic effects have been reported with dietary capsaicin intakes in the range of 0.01–0.02% of diet. If a human were to eat (say) 400 g dry weight of food daily, 0.01% of diet would correspond to 40 mg capsaicin. Oral administration of capsaicin represents a clinical challenge—many people, especially those not acclimated to a spicy diet, do not enjoy the oral pain associated with capsaicin-laced foods, and capsaicin capsules may cause GI distress in some persons; this latter effect is mitigated somewhat by ingesting capsaicin capsules with meals. When Lejeune *et al*[77] had study volunteers take 45 mg capsaicin three times daily with meals, 24% of them experienced significant stomach discomfort and were allowed to cut this dose in half; however, this dose regimen seems likely to be a higher dose than would be required for metabolic benefits.

Hot peppers typically contain capsaicin in conjunction with lesser amounts of its analogues, dihydrocapsaicin and nordihydrocapsaicin; the latter is a very minor component, but dihyrocapsaicin may constitute as much as 40% of total capsaicinoids. The relative proportion of

Table 1 Health benefits of capsaicin administration suggested by preclinical and clinical research

Condition benefited	Likely mechanisms of action
Atherosclerosis[26 29 30]	Improved endothelial function, including eNOS activation/induction; induction of LXRalpha in foam cells, promoting cholesterol export
Diabetic vasculopathy[39]	Induction of UCP2 and eNOS in endothelium
Stroke[28]	Improved endothelial function, including eNOS activation/induction
Angina[31]	Improved endothelium-dependent vasodilation of coronary arteries
Hypertension[27 32 33]	Activation/induction of eNOS; decreased renal sodium retention
Metabolic syndrome[54–58]	Decreased adipose inflammation—reflecting PPARgamma induction
Cardiac hypertrophy[41]	Induction of PPARdelta
Fatty liver[39 52]	Induction of UCP2 in hepatocytes; decreased adipose inflammation Increased GLP-1 secretion
Obesity[56 57 61 62 66]	Sympathetic activation of brown fat thermogenesis Improved appetite control—vagal signal to appetite centers, ↑ GLP-1; increased adipocyte capacity for lipolysis
Gastric ulceration[68–70]	Decreased acid secretion; increased alkali; increased gastric blood flow

eNOS, endothelial nitric oxide synthase; GLP-1, glucagon-like peptide-1; UCP2, uncoupling protein 2

capsaicin and dihydrocapsaicin in a food is of little practical import, as the abilities of these compounds to activate TRPV1 are roughly equivalent. Commercial capsules of cayenne pepper are available that provide 40 000–100 000 Scoville heat units per capsule. The Scoville scale quantifies the spicy heat (or pungency) of foods which contain capsaicinoids; a gram of capsaicin corresponds to 16 million Scoville heat units; a gram of dihydrocapsaicin to 15 million units; and a gram of nordihydrocapsaicin to 9.1 million units. Therefore, a capsule claiming 100 000 Scoville heat units can be expected to contain about 6.6 mg of capsaicinoids. Consuming three of these daily with meals will provide about 20 mg, and those who enjoy spicy foods could supplement this with peppers, pepper sauces, or cayenne powder added to foods. Perhaps this would be an appropriate 'baseline' regimen to study clinically. Topical administration of capsaicin in patches may represent a reasonable alternative in people unable to tolerate it orally—albeit this will be a more expensive option, and local pain is commonly experienced for an hour or more after patch application.[78]

EXPLORING THE HEALTH POTENTIAL OF CAPSAICIN

This brief overview should make it clear that dietary capsaicin—and, likely to a more limited degree, nonpungent capsiate—has intriguing potential for health promotion. Rodent studies suggest that capsaicin may merit clinical evaluation with respect to endothelial function, progression of atherosclerosis (most notably in diabetics), angina, non-alcoholic fatty liver disease, cardiac hypertrophy, metabolic syndrome, hypertension, obesity and gastric ulceration. (See table 1 for a summary of these potential benefits and the mechanisms that may underlie them.) In addition to the many studies assessing capsaicin's impact on metabolic rate and adiposity, the trial of topical capsaicin in patients with angina, and the studies documenting capsaicin's gastroprotective effects, represent initial efforts in this regard. A study examining endothelium-dependent vasodilation in diabetics might be particularly useful, as a systemically adequate dose of capsaicin could be expected to have a notably favourable impact on this parameter. Assessment of the dose-dependency of this effect could provide useful insight into capsaicin clinical dosage schedules which could provide systemic metabolic benefits. Both oral and topical application of capsaicin could be tested in this regard. The rodent literature is sufficiently intriguing that serious efforts to evaluate the feasibility of capsaicin administration as a clinical or lifestyle strategy appear to be warranted. However, owing to the fact that TRPV1 receptors are expressed on a wide range of tissues, the possibility that high-dose capsaicin might exert unanticipated or unwanted physiological effects should be borne in mind.

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Competing interests JJD works for a company that sells capsaicin products, but he has no direct role in marketing or selling them. JHO'K and MFMC have ownership interests in companies that make nutritional supplements, but these companies do not sell capsaicin products.

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REFERENCES

1. Zsombok A. Vanilloid receptors—do they have a role in whole body metabolism? Evidence from TRPV1. *J Diabetes Complications* 2013;27:287–92.
2. Nilius B, Szallasi A. Transient receptor potential channels as drug targets: from the science of basic research to the art of medicine. *Pharmacol Rev* 2014;66:676–814.
3. Zhu Z, Luo Z, Ma S, *et al*. TRP channels and their implications in metabolic diseases. *Pflugers Arch* 2011;461:211–23.
4. Iida T, Moriyama T, Kobata K, *et al*. TRPV1 activation and induction of nociceptive response by a non-pungent capsaicin-like compound, capsiate. *Neuropharmacology* 2003;44:958–67.

5. Kawada T, Suzuki T, Takahashi M, *et al*. Gastrointestinal absorption and metabolism of capsaicin and dihydrocapsaicin in rats. *Toxicol Appl Pharmacol* 1984;72:449–56.
6. Rollyson WD, Stover CA, Brown KC, *et al*. Bioavailability of capsaicin and its implications for drug delivery. *J Control Release* 2014;196:96–105.
7. Chaiyasit K, Khovidhunkit W, Wittayalertpanya S. Pharmacokinetic and the effect of capsaicin in Capsicum frutescens on decreasing plasma glucose level. *J Med Assoc Thai* 2009;92:108–13.
8. Kopanitsa MV, Panchenko VA, Magura EI, *et al*. Capsaicin blocks Ca2+channels in isolated rat trigeminal and hippocampal neurones. *Neuroreport* 1995;6:2338–40.
9. Sim JH, Kim YC, Kim SJ, *et al*. Capsaicin inhibits the voltage-operated calcium channels intracellularly in the antral circular myocytes of guinea-pig stomach. *Life Sci* 2001;68:2347–60.
10. Vyklicky L, Novakova-Tousova K, Benedikt J, *et al*. Calcium-dependent desensitization of vanilloid receptor TRPV1: a mechanism possibly involved in analgesia induced by topical application of capsaicin. *Physiol Res* 2008;57(Suppl 3):S59–68.
11. Kissin I. Vanilloid-induced conduction analgesia: selective, dose-dependent, long-lasting, with a low level of potential neurotoxicity. *Anesth Analg* 2008;107:271–81.
12. Knotkova H, Pappagallo M, Szallasi A. Capsaicin (TRPV1 Agonist) therapy for pain relief: farewell or revival? *Clin J Pain* 2008;24:142–54.
13. Jones VM, Moore KA, Peterson DM. Capsaicin 8% topical patch (Qutenza)—a review of the evidence. *J Pain Palliat Care Pharmacother* 2011;25:32–41.
14. Gunthorpe MJ, Szallasi A. Peripheral TRPV1 receptors as targets for drug development: new molecules and mechanisms. *Curr Pharm Des* 2008;14:32–41.
15. Czikora A, Rutkai I, Pasztor ET, *et al*. Different desensitization patterns for sensory and vascular TRPV1 populations in the rat: expression, localization and functional consequences. *PLoS ONE* 2013;8:e78184.
16. Fleming I, Busse R. Signal transduction of eNOS activation. *Cardiovasc Res* 1999;43:532–41.
17. Chen Z, Peng IC, Cui X, *et al*. Shear stress, SIRT1, and vascular homeostasis. *Proc Natl Acad Sci U S A* 2010;107:10268–73.
18. Young A, Wu W, Sun W, *et al*. Flow activation of AMP-activated protein kinase in vascular endothelium leads to Kruppel-like factor 2 expression. *Arterioscler Thromb Vasc Biol* 2009;29:1902–8.
19. Wang W, Ha CH, Jhun BS, *et al*. Fluid shear stress stimulates phosphorylation-dependent nuclear export of HDAC5 and mediates expression of KLF2 and eNOS. *Blood* 2010;115:2971–9.
20. Parmar KM, Larman HB, Dai G, *et al*. Integration of flow-dependent endothelial phenotypes by Kruppel-like factor 2. *J Clin Invest* 2006;116:49–58.
21. SenBanerjee S, Lin Z, Atkins GB, *et al*. KLF2 Is a novel transcriptional regulator of endothelial proinflammatory activation. *J Exp Med* 2004;199:1305–15.
22. Lin Z, Kumar A, SenBanerjee S, *et al*. Kruppel-like factor 2 (KLF2) regulates endothelial thrombotic function. *Circ Res* 2005;96:e48–57.
23. Fledderus JO, van Thienen JV, Boon RA, *et al*. Prolonged shear stress and KLF2 suppress constitutive proinflammatory transcription through inhibition of ATF2. *Blood* 2007;109:4249–57.
24. Fledderus JO, Boon RA, Volger OL, *et al*. KLF2 primes the antioxidant transcription factor Nrf2 for activation in endothelial cells. *Arterioscler Thromb Vasc Biol* 2008;28:1339–46.
25. Lo YC, Hsiao HC, Wu DC, *et al*. A novel capsaicin derivative VOA induced relaxation in rat mesenteric and aortic arteries: involvement of CGRP, NO, cGMP, and endothelium-dependent activities. *J Cardiovasc Pharmacol* 2003;42:511–20.
26. Ching LC, Kou YR, Shyue SK, *et al*. Molecular mechanisms of activation of endothelial nitric oxide synthase mediated by transient receptor potential vanilloid type 1. *Cardiovasc Res* 2011;91:492–501.
27. Yang D, Luo Z, Ma S, *et al*. Activation of TRPV1 by dietary capsaicin improves endothelium-dependent vasorelaxation and prevents hypertension. *Cell Metab* 2010;12:130–41.
28. Xu X, Wang P, Zhao Z, *et al*. Activation of transient receptor potential vanilloid 1 by dietary capsaicin delays the onset of stroke in stroke-prone spontaneously hypertensive rats. *Stroke* 2011;42:3245–51.
29. Ma L, Zhong J, Zhao Z, *et al*. Activation of TRPV1 reduces vascular lipid accumulation and attenuates atherosclerosis. *Cardiovasc Res* 2011;92:504–13.
30. Zhao JF, Ching LC, Kou YR, *et al*. Activation of TRPV1 prevents OxLDL-induced lipid accumulation and TNF-alpha-induced inflammation in macrophages: role of liver X receptor alpha. *Mediators Inflamm* 2013;2013:925171.
31. Fragasso G, Palloshi A, Piatti PM, *et al*. Nitric-oxide mediated effects of transdermal capsaicin patches on the ischemic threshold in patients with stable coronary disease. *J Cardiovasc Pharmacol* 2004;44:340–7.
32. Hao X, Chen J, Luo Z, *et al*. TRPV1 activation prevents high-salt diet-induced nocturnal hypertension in mice. *Pflugers Arch* 2011;461:345–53.
33. Li L, Wang F, Wei X, *et al*. Transient receptor potential vanilloid 1 activation by dietary capsaicin promotes urinary sodium excretion by inhibiting epithelial sodium channel alpha subunit-mediated sodium reabsorption. *Hypertension* 2014;64:397–404.
34. Bratz IN, Dick GM, Tune JD, *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.
35. Zygmunt PM, Petersson J, Andersson DA, *et al*. Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide. *Nature* 1999;400:452–7.
36. Czikora A, Lizanecz E, Bako P, *et al*. Structure-activity relationships of vanilloid receptor agonists for arteriolar TRPV1. *Br J Pharmacol* 2012;165:1801–12.
37. Patane S, Marte F, La Rosa FC, *et al*. Capsaicin and arterial hypertensive crisis. *Int J Cardiol* 2010;144:e26–7.
38. Dutta A, Deshpande SB. Mechanisms underlying the hypertensive response induced by capsaicin. *Int J Cardiol* 2010;145:358–9.
39. Sun J, Pu Y, Wang P, *et al*. TRPV1-mediated UCP2 upregulation ameliorates hyperglycemia-induced endothelial dysfunction. *Cardiovasc Diabetol* 2013;12:69.
40. Li L, Chen J, Ni Y, *et al*. TRPV1 activation prevents nonalcoholic fatty liver through UCP2 upregulation in mice. *Pflugers Arch* 2012;463:727–32.
41. Gao F, Liang Y, Wang X, *et al*. TRPV1 activation attenuates high-salt diet-induced cardiac hypertrophy and fibrosis through PPAR-delta upregulation. *PPAR Res* 2014;2014:491963.
42. Planavila A, Rodriguez-Calvo R, Jove M, *et al*. Peroxisome proliferator-activated receptor beta/delta activation inhibits hypertrophy in neonatal rat cardiomyocytes. *Cardiovasc Res* 2005;65:832–41.
43. Negre-Salvayre A, Hirtz C, Carrera G, *et al*. A role for uncoupling protein-2 as a regulator of mitochondrial hydrogen peroxide generation. *FASEB J* 1997;11:809–15.
44. Echtay KS, Roussel D, St-Pierre J, *et al*. Superoxide activates mitochondrial uncoupling proteins. *Nature* 2002;415:96–9.
45. Echtay KS, Brand MD. 4-hydroxy-2-nonenal and uncoupling proteins: an approach for regulation of mitochondrial ROS production. *Redox Rep* 2007;12:26–9.
46. Piconi L, Quagliaro L, Assaloni R, *et al*. Constant and intermittent high glucose enhances endothelial cell apoptosis through mitochondrial superoxide overproduction. *Diabetes Metab Res Rev* 2006;22:198–203.
47. Nishikawa T, Kukidome D, Sonoda K, *et al*. Impact of mitochondrial ROS production on diabetic vascular complications. *Diabetes Res Clin Pract* 2007;77(Suppl 1):S41–5.
48. Tian XY, Wong WT, Xu A, *et al*. Uncoupling protein-2 protects endothelial function in diet-induced obese mice. *Circ Res* 2012;110:1211–16.
49. Cheurfa N, Dubois-Laforgue D, Ferrarezi DA, *et al*. The common -866G>A variant in the promoter of UCP2 is associated with decreased risk of coronary artery disease in type 2 diabetic men. *Diabetes* 2008;57:1063–8.
50. Serviddio G, Sastre J, Bellanti F, *et al*. Mitochondrial involvement in non-alcoholic steatohepatitis. *Mol Aspects Med* 2008;29:22–35.
51. Serviddio G, Bellanti F, Tamborra R, *et al*. Uncoupling protein-2 (UCP2) induces mitochondrial proton leak and increases susceptibility of non-alcoholic steatohepatitis (NASH) liver to ischaemia-reperfusion injury. *Gut* 2008;57:957–65.
52. Li Q, Li L, Wang F, *et al*. Dietary capsaicin prevents nonalcoholic fatty liver disease through transient receptor potential vanilloid 1-mediated peroxisome proliferator-activated receptor delta activation. *Pflugers Arch* 2013;465:1303–16.
53. McCarty MF. High mitochondrial redox potential may promote induction and activation of UCP2 in hepatocytes during hepatothermic therapy. *Med Hypotheses* 2005;64:1216–19.
54. Kang JH, Kim CS, Han IS, *et al*. 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.
55. Kang JH, Tsuyoshi G, Le NH, *et al*. Dietary capsaicin attenuates metabolic dysregulation in genetically obese diabetic mice. *J Med Food* 2011;14:310–15.

56. Lee GR, Shin MK, Yoon DJ, *et al*. Topical application of capsaicin reduces visceral adipose fat by affecting adipokine levels in high-fat diet-induced obese mice. *Obesity (Silver Spring)* 2013;21:115–22.
57. Chen J, Li L, Li Y, *et al*. Activation of TRPV1 channel by dietary capsaicin improves visceral fat remodeling through connexin43-mediated Ca2+Influx. *Cardiovasc Diabetol* 2015;14:22.
58. Wang P, Yan Z, Zhong J, *et al*. Transient receptor potential vanilloid 1 activation enhances gut glucagon-like peptide-1 secretion and improves glucose homeostasis. *Diabetes* 2012;61:2155–65.
59. Kawabata F, Inoue N, Masamoto Y, *et al*. Non-pungent capsaicin analogs (capsinoids) increase metabolic rate and enhance thermogenesis via gastrointestinal TRPV1 in mice. *Biosci Biotechnol Biochem* 2009;73:2690–7.
60. Ono K, Tsukamoto-Yasui M, Hara-Kimura Y, *et al*. Intragastric administration of capsiate, a transient receptor potential channel agonist, triggers thermogenic sympathetic responses. *J Appl Physiol (1985)* 2011;110:789–98.
61. Ludy MJ, Moore GE, Mattes RD. The effects of capsaicin and capsiate on energy balance: critical review and meta-analyses of studies in humans. *Chem Senses* 2012;37:103–21.
62. Whiting S, Derbyshire EJ, Tiwari B. Could capsaicinoids help to support weight management? A systematic review and meta-analysis of energy intake data. *Appetite* 2014;73:183–8.
63. Yoneshiro T, Aita S, Kawai Y, *et al*. Nonpungent capsaicin analogs (capsinoids) increase energy expenditure through the activation of brown adipose tissue in humans. *Am J Clin Nutr* 2012;95:845–50.
64. Saito M, Yoneshiro T. Capsinoids and related food ingredients activating brown fat thermogenesis and reducing body fat in humans. *Curr Opin Lipidol* 2013;24:71–7.
65. Shirai Y, Ueno S, Nakayama A, *et al*. Studies of the toxicological potential of capsinoids, XII: pharmacokinetic study of capsinoid-containing CH-19 Sweet extract in rats. *Int J Toxicol* 2010;29(2 Suppl):15S–21S.
66. Snitker S, Fujishima Y, Shen H, *et al*. Effects of novel capsinoid treatment on fatness and energy metabolism in humans: possible pharmacogenetic implications. *Am J Clin Nutr* 2009;89:45–50.
67. Yoneshiro T, Saito M. Transient receptor potential activated brown fat thermogenesis as a target of food ingredients for obesity management. *Curr Opin Clin Nutr Metab Care* 2013;16:625–31.
68. Satyanarayana MN. Capsaicin and gastric ulcers. *Crit Rev Food Sci Nutr* 2006;46:275–328.
69. Mozsik G. Capsaicin as new orally applicable gastroprotective and therapeutic drug alone or in combination with nonsteroidal anti-inflammatory drugs in healthy human subjects and in patients. *Prog Drug Res* 2014;68:209–58.
70. Sandor B, Papp J, Mozsik G, *et al*. Orally given gastroprotective capsaicin does not modify aspirin-induced platelet aggregation in healthy male volunteers (human phase I examination). *Acta Physiol Hung* 2014;101:429–37.
71. Pabalan N, Jarjanazi H, Ozcelik H. The impact of capsaicin intake on risk of developing gastric cancers: a meta-analysis. *J Gastrointest Cancer* 2014;45:334–41.
72. Bley K, Boorman G, Mohammad B, *et al*. A comprehensive review of the carcinogenic and anticarcinogenic potential of capsaicin. *Toxicol Pathol* 2012;40:847–73.
73. Nan HM, Park JW, Song YJ, *et al*. Kimchi and soybean pastes are risk factors of gastric cancer. *World J Gastroenterol* 2005;11:3175–81.
74. Seel DJ, Kawabata T, Nakamura M, *et al*. N-nitroso compounds in two nitrosated food products in southwest Korea. *Food Chem Toxicol* 1994;32:1117–23.
75. D'Elia L, Galletti F, Strazzullo P. Dietary salt intake and risk of gastric cancer. *Cancer Treat Res* 2014;159:83–95.
76. Gaddy JA, Radin JN, Loh JT, *et al*. High dietary salt intake exacerbates Helicobacter pylori-induced gastric carcinogenesis. *Infect Immun* 2013;81:2258–67.
77. Lejeune MP, Kovacs EM, Westerterp-Plantenga MS. Effect of capsaicin on substrate oxidation and weight maintenance after modest body-weight loss in human subjects. *Br J Nutr* 2003;90:651–9.
78. Peppin JF, Majors K, Webster LR, *et al*. Tolerability of NGX-4010, a capsaicin 8% patch for peripheral neuropathic pain. *J Pain Res* 2011;4:385–92.