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Obesity Management/Pharmacotherapy

Transient receptor potential (TRP) channels: a metabolic TR(i)P to obesity prevention and therapy

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Summary

Cellular transport of ions, especially by ion channels, regulates physiological function. The transient receptor potential (TRP) channels, with 30 identified so far, are cation channels with high calcium permeability. These ion channels are present in metabolically active tissues including adipose tissue, liver, gastrointestinal tract, brain (hypothalamus), pancreas and skeletal muscle, which suggests a potential role in metabolic disorders including obesity. TRP channels have potentially important roles in adipogenesis, obesity development and its prevention and therapy because of their physiological properties including calcium permeability, thermosensation and taste perception, involvement in cell metabolic signalling and hormone release. This wide range of actions means that organ-specific actions are unlikely, thus increasing the possibility of adverse effects. Delineation of responses to TRP channels has been limited by the poor selectivity of available agonists and antagonists. Food constituents that can modulate TRP channels are of interest in controlling metabolic status. TRP vanilloid 1 channels modulated by capsaicin have been the most studied, suggesting that this may be the first target for effective pharmacological modulation in obesity. This review shows that most of the TRP channels are potential targets to reduce metabolic disorders through a range of mechanisms.

Keywords: adipocytes, energy expenditure, obesity, transient receptor potential channel.

Abbreviations: BAT, brown adipose tissue; CGRP, calcitonin gene-related peptide; GLP-1, glucagon-like peptide 1; POMC, proopiomelanocortin; TRP, transient receptor potential; WAT, white adipose tissue; thermo-TRP, thermosensitive TRP channels.

Introduction

Obesity has become an important health concern worldwide. Analysis of data from 188 countries between 1990 and 2013 showed that nearly 30% of the world's population or 2.1 billion people were either obese or overweight (1). During this period, the rise in rate of obesity and overweight has been substantial for both men, from 28.8% to 36.9%, and women, from 29.8% to 38%. Moreover, the nearly 47% increase in prevalence in children and adolescents of overweight or obesity during this period indicates that obesity will continue as a cause of ill-health for many decades to come (1). The overall burden of healthcare costs for obesity and its related complications will continue to increase, as complications are life-threatening, such as cardiovascular complications, insulin resistance and type-2 diabetes, dyslipidaemia, cancer, osteoarthritis and chronic kidney disease (2–5). The most important causal factor of obesity is an imbalance in energy intake and energy expenditure, with energy-dense diets playing a major role in this imbalance. Insufficient physical activity and sleep, endocrine disruption, altered thermoneutrality,

smoking cessation, use of antipsychotic drugs, pregnancy in later stage, genetic and epigenetic risk factors are some of the changes that increase the storage of excess energy by the body (6).

Bariatric surgery, including gastric bypass surgery, laparoscopic adjustable gastric banding, biliopancreatic diversion with duodenal switch and gastric sleeve, is the most effective treatment option for obesity, but it is highly invasive and often associated with major post-operative complications (7,8). Over the years, many anti-obesity medications have been developed for the management of obesity, but most have been withdrawn (9). These medications reduce or control weight by affecting one or more of the fundamental physiological processes of hunger and satiety by controlling neuronal and hormonal signals. Because these processes are essential for growth and development, these medications contain the potential for adverse effects, including cardiovascular and neurological complications (10–17). There are many anti-obesity medications in the drug development pipeline, with the most promising drugs being co-agonists for multiple gut hormones including glucagon-like peptide 1 (GLP-1), glucagon and gastric inhibitory peptide (18). The GLP-1 analogue, liraglutide, has shown its anti-obesity effects in many clinical trials (15,19,20), but it needs to be injected subcutaneously daily and is very expensive (21). There is a long way to go before we will be able to establish efficacy and safety with chronic therapy with these novel agents (22). The experience with anti-obesity drugs has produced well-founded cynicism about new drugs. Given the rapid development and major risks of the current obesity epidemic, how long can we wait for effective and safe treatments?

The marked increase in prevalence of obesity and overweight across all countries, genders and age groups accompanied by the withdrawal of pharmaceutical therapeutics for obesity has encouraged researchers to look at different therapeutic targets for tolerable, easy to administer and more effective alternatives to manage obesity as a chronic disease. The transient receptor potential (TRP) family is a potential candidate to regulate energy homeostasis as these channels are major contributors to many physiological conditions associated with energy balance, gut hormone release, adipokine secretion, gut-brain axis modulation and glucose homeostasis. The present review summarises the functional role of TRP channels and food constituents modulating these channels in obesity.

Transient receptor potential family

More than 30 mammalian TRP channels have been cloned and characterised (23,24). These are classified by their sequence homology, rather than by ligand function or ion selectivity as with other ion channels, into seven subfamilies of TRP channels in mammals – TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPA (ankyrin), TRPP (polycystin), TRPML (mucolipin) and TRPN (*Drosophila* no mechanoreceptor potential C). In yeast, an eighth TRP family, TRPY (yeast), has been identified (23). There are many highly non-specific blockers of TRP channels with relatively few selective agonists such as capsaicin on TRPV1 channels, making the correlation of receptors and responses much more difficult (24). TRP channels are expressed in neuronal and non-neuronal tissues and are critical for physiological functions such as senses (vision, taste perception, hearing, olfaction, nociception, mechanosensation and thermosensation), homeostasis (absorption and reabsorption of ions and fluid flow) and cell survival and growth (25–28). Additionally, the presence of these channels in tissues such as the hypothalamus, adipocytes, liver, intestine and pancreas that influence energy intake, storage and expenditure together with evidence from various *in vitro* and *in vivo* (diet-induced obesity and knockout) studies suggested the role of TRP channels in regulating energy homeostasis (29–32). Three important characteristics of TRP channels, calcium permeability, thermosensation and mechanosensation, together with the modulation of these channels by dietary constituents, make them an attractive target for regulation of metabolic function and energy uptake.

Calcium permeability

Most of the TRP channels are located at the plasma membrane with high permeability to calcium, a versatile signalling molecule regulating many cellular processes (27). Calcium has been implicated as a critical mediator in cellular mechanisms associated with obesity, in general, and adipogenesis, in particular (33). Using *Drosophila* as a model organism, calcium signalling influences lipid storage and lysis in cells (34–37). The role of calcium is biphasic, with an acute increase inducing lipolysis in adipocytes but a chronic increase inhibiting lipolysis (38,39). *In vitro* studies showed that elevated calcium concentrations inhibited differentiation markers and lipid accumulation in murine 3T3-L1 pre-adipocytes and human adipocytes *via* G-protein-coupled mechanisms mediated by a novel calcium sensor or receptor (40–43). Calcium-dependent molecular activity mediated by calcineurin, a calcium-dependent serine-threonine phosphatase, and calreticulin may inhibit adipocyte differentiation (44,45). Furthermore, increasing cytosolic calcium affects multiple transcription factors regulating hormonal and non-hormonal activities responsible for adipocyte differentiation, functions such as adipokine release and thermogenic ability, and survival (46–49). Increasing extracellular calcium decreases brown adipose tissue (BAT) differentiation and thermogenic ability (50). Also, intracellular calcium ions

modulate insulin and leptin signalling in adipocytes (51,52). Considering the importance of calcium in adipocyte biology, it is essential to unravel the function of TRP channels as the most significant calcium-permeable channels in adipocytes (33).

Pancreatic islets produce insulin in β-cells and glucagon in α-cells, with these two important hormones having opposite effects on plasma glucose concentrations and hence regulation of metabolism. Molecular and physiological *in vivo* and cell-based studies have shown the presence of voltage-gated calcium channels with β-cells containing dihydropyridine-sensitive Ca^{2+}-channels, SNX482-sensitive R-type Ca^{2+}-channels, P/Q type Ca^{2+}-channels, L-type Ca^{2+}-channels containing α1C (Cav1.2) and α1D (Cav1.3) pore-forming subunits and T-type Ca^{2+}-channels while α-cells contain T-type Ca^{2+}-channels, L- (80%) and N-type HVA Ca^{2+}-channels (53–56). These studies have also defined the role of intracellular calcium in insulin and glucagon release (57,58). Increased glucose concentrations lead to a concentration-dependent reduction in K_{ATP}-channel activity followed by depolarisation and action potential firing. The action potentials involve activation of voltage-gated L-type Ca^{2+}-channels and other Ca^{2+}-entry pathways leading to stimulation of Ca^{2+}-dependent exocytosis of the insulin-containing secretory granules, hence insulin secretion (59–61). Glucose-mediated amplifying effects on secretory granules require calcium to release insulin and glucagon in pancreatic islets (61–63).

Mammalian skeletal muscle is central to energy metabolism through its response to many factors including growth and differentiation factors, hormones, nerve signals and exercise (64,65). All muscle fibre use calcium as their main regulatory (contraction and relaxation) and signalling (regulation of protein metabolism, differentiation and growth) molecule. The calcium cycle in skeletal muscle includes the ryanodine receptor (the sarcoplasmic reticular Ca^{2+}-release channel), the troponin protein complex, the Ca^{2+}-pump for sarcoplasmic reticulum re-uptake of calcium, and calsequestrin, the Ca^{2+}-storage protein (66–68). There are many other proteins present in muscle tissues such as parvalbumin, calmodulin, S100 proteins, annexins, sorcin, myosin light chains, β-actinin, calcineurin and calpain that regulate or modulate the calcium-dependent muscle contractile activity (69). Exercise-induced increases in skeletal muscle activity and release of specific hormones are associated with energy regulation and expenditure (70). Skeletal muscle, unlike other cell types, contains unique voltage-gated calcium channels, which on opening do not increase intracellular calcium but instead initiate the opening of ryanodine receptors allowing calcium entry to the sarcoplasmic reticulum (71). Cytosolic Ca^{2+} and its related mediators, channels and pathways are the major mediators of glucose uptake in skeletal muscles. Calcium signalling serves as a major mediator of muscle function. Increased cytosolic calcium and muscle contraction increase the mitochondrial biogenesis, mitochondrial energy expenditure, GLUT4 expression in muscles and glucose uptake (72–75). Although voltage-gated calcium channels are the major calcium channels present in skeletal muscles, multiple TRP channels are also present. Understanding the control of these calcium-permeable TRP channels during energy regulation is important as calcium plays such an important role in adipocyte biology, insulin and glucagon release and skeletal muscle activity.

Thermosensitive transient receptor potential channels

There are 11 thermosensitive TRP channels (thermo-TRP) so far identified in mammals (31). These channels, members of TRPV, TRPM, TRPA and TRPC subfamilies, have temperature thresholds for activation in physiological ranges (Fig. 1). TRPV1 (>42°C) and TRPV2 (>52°C) are activated by heat; TRPV3 (>32°C), TRPV4 (>27–41°C), TRPM2 (>36°C), TRPM4 (15–35°C) and TRPM5 (15–35°C) are activated around mammalian body temperature while TRPM8 (<27°C) and TRPA1 (<17°C) are sensors of lower temperature (31). TRPM3 (40°C) and TRPC5 (<35–25°C) are included as thermo-TRPs as they sense warm and cold temperatures, respectively (76,77). Some of these thermo-TRP channels are expressed in sensory neurons and skin, making them crucial to detect links between environmental temperatures and metabolism (31).

Apart from food habits and physical activity, habitat environmental temperature plays an important role in mammalian energy balance. In thermo-neutral ambient conditions, the human body requires minimal heat production from available energy sources to achieve core body temperature. Altered habitat temperature, above or below the thermo-neutral temperature, can enhance resting energy expenditure (78). Decreased resting energy expenditure in thermo-neutral indoor housing may be one of the contributing factors in the development of obesity (79). Cold is a natural stimulus for adaptive thermogenesis and resultant energy expenditure (80,81). An increased energy expenditure of 105 to 156 kJ d^{-1}/1°C is required to maintain core body temperature in ambient temperature below thermo-neutral temperature (79,82). In the pioneering studies on cold-induced resting energy expenditure, ambient temperatures below 16.2°C increased the resting energy expenditure by 36% as compared with thermo-neutral ambient temperature in terms of CO_2 production (83). The detection of thermal stimuli occurs with the help of neuronal cells located in the dorsal root ganglia and cranial nerve ganglia. Axons of these sensory neurons travel through the peripheral sites of skin and terminate as a free nerve terminal to detect the stimuli and relay this information to the spinal cord (84). Many mechanisms and

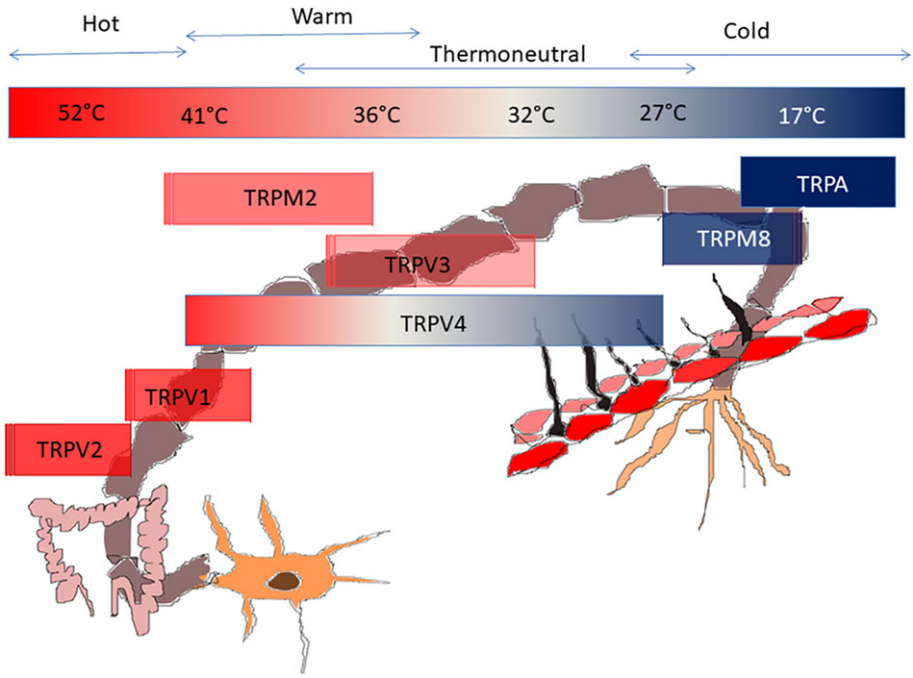

Figure 1 Thermo-TRP channels and their activation temperatures. TRP, transient receptor potential; TRPA, TRP ankyrin; TRPM, TRP melastatin; TRPV, TRP vanilloid. [Colour figure can be viewed at wileyonlinelibrary.com]

receptors are thought to be responsible for thermosensation at the free nerve terminals present at different thermosensory locations, of which TRP ion channels are the most important (Fig. 1) (84).

Other endogenous and environmental stimuli also modulate thermo-TRP channels. TRP channels sensed oxygen concentrations in hypoxia (TRPA1, TRPM2, TRPM7, TRPC1, TRPC3, TRPC6, TRPV1 and TRPV4) while TRPA1 channels also directly sensed oxygen concentrations in hyperoxia (85,86). TRPM7, TRPA1 and TRPV1 channels were also activated by reactive oxygen species (87,88), and TRPA1 channels were also activated by UV light (89). TRP channels can also be activated by mechanostimulation. TRPC1 channel activation was achieved by applying pressure (90), while TRPM7 and TRPM4 channels were sensitive to membrane stretch (91–93). TRPV2 and TRPC6 were activated by changes in osmotic pressure (94–96).

Modulation of transient receptor potential channels by natural compounds and dietary constituents

Transient receptor potential channels are modulated by food and dietary constituents, making them a viable option for developing individual food-based strategies to prevent obesity. However, the concept that dietary constituents will reduce obesity remains intuitive and possible rather than proven (97). The development of personalised nutrition with analysis and monitoring of dietary habits, food behaviour and physical activity and exercise, including nutrigenomics, metabolomics and microbiota profiling, may be successful in implementing innovative precision nutrition approaches to metabolic syndrome (98). The difficulty in complying with long-term personalised nutrition, including consuming sufficient amounts of effective dietary constituents, suggests that improved approaches to diet-based treatments for obesity are needed. TRP channels modulated by compounds available in foods include TRPV1 (capsaicin from chillies, piperine from black pepper, gingerol from ginger, eugenol from clove and capsinoids), TRPA1 (cinnamaldehyde from cinnamon, allicin from garlic and onion, allyl isothiocyanate from wasabi and phenylethyl isothiocyanate from brussels sprouts), TRPV2 (Δ^9-tetrahydro-cannabinol and cannabinol from cannabis), TRPM8 (menthone and menthol from mint, eucalyptol from essential oils from *Eucalyptus polybractea*, geraniol from lemongrass and aromatic herb oils, L-carvone from spearmint or Kuromoji oil and hydroxyl-citronellal from citronella oils, volatile oils such as lemon, lemongrass or melissa oils), TRPM5 (steviol glycosides from stevia), TRPV3 (thymol from thyme and carvacrol from clove), TRPC6 (hyperforin from St John's Wort) and TRPC1/5 (omega-3 polyunsaturated fatty acids such as α-linolenic acid, docosahexaenoic acid and eicosapentaenoic acid) (33,99–101). This leads to the hypothesis that TRP channel-mediated responses to these natural products or foods can improve metabolism.

Involvement of different transient receptor potential channels in obesity

Transient receptor potential vanilloid 1 channels

Transient receptor potential vanilloid 1, the most studied receptor of the TRP channel family, is a homotetrameric non-selective cation channel with high permeability to calcium ions (102), where the central pore, formed by a hydrophobic section between the fifth and sixth transmembrane domains (S5–S6), is surrounded by four subunits and a pore-loop flanked by S1–S4 transmembrane domains (103,104). This channel is primarily expressed in a population of sensory neurons, and its involvement in different modalities of pain has been extensively studied and reviewed (102,105,106). It is activated by numerous chemicals including capsaicin, piperine and endogenous lipids including anandamide and by physical stimuli such as low pH and temperatures above 42°C (101,107–109). It is also expressed in other neuronal and non-neuronal tissues, which suggests its functional role in many intercellular and extracellular physiological processes and regulatory mechanisms (110–113).

Transient receptor potential vanilloid 1 channels are present in 3T3-L1 pre-adipocytes and adipocytes and in both human and murine visceral adipose tissue (114). The expression of TRPV1 channels was higher in pre-adipocytes and lower in adipocytes during adipocyte differentiation using calcium influx assays. TRPV1 expression was decreased in visceral adipose tissue from obese, *db*/*db* and *ob*/*ob* mice, and from human males with obesity (114). Selective silencing of TRPV1 using specific RNA interference reduced the actions of capsaicin both on calcium influx and inhibition of adipogenesis in 3T3-L1 adipocytes (114). In 3T3-L1 preadipocytes and adipocytes, lower-dose capsaicin decreased expression of PPAR-γ, C/EBP-α and leptin, induced apoptosis (115), inhibited adipogenesis, induced anti-adipogenic genes and promoted brite phenotype by a TRPV1-dependent mechanism (116). At higher doses, capsaicin promoted adipogenesis associated with decreased expression of anti-adipogenic and BAT-specific genes (116). Further, higher-dose capsaicin decreased inflammatory marker production in adipocytes (116).

Capsaicin induced anti-obesity responses through different TRPV1-dependent mechanisms including inhibition of adipogenesis, browning of white adipose tissue (WAT), activation of BAT and alteration of hypothalamic gene expression (117). The anti-obesity effects of capsaicin relate to its actions on TRPV1 channels as diet-induced obesity was prevented in wild-type mice by capsaicin but not in TRPV1-knockout mice (114). Oral capsaicin prevented obesity-induced glucose intolerance in high-fat diet-fed C57BL/6 obese mice by suppressing inflammation and enhancing fatty acid oxidation (lipolysis) in adipose tissue and liver (118). Oral administration of capsaicin (2 mg kg^{-1} d^{-1} for 12 weeks) modulated hypothalamic satiety-associated genotype, induced browning genotype (BAT-associated genes) in subcutaneous WAT and increased expression of genes related to thermogenesis and mitochondrial biogenesis in BAT (117). TRPV1 activation by capsaicin promoted lipolysis and improved visceral fat remodelling in both mice and humans through Cx43-mediated increase in extracellular Ca^{2+} influx (119). In TRPV1 knockout mice, TRPV1 channels played a major role in hypothalamic leptin activity and glucose homeostasis because of altered STAT-3 activity (120). Capsaicin triggered browning of WAT by promoting sirtuin-1 expression and activity through TRPV1-dependent mechanisms such as enhanced intracellular Ca^{2+} concentrations and phosphorylation of Ca^{2+}/calmodulin-activated protein kinase II and AMP-activated protein kinase (121). Capsaicin activation of TRPV1 in BAT enhanced the expression of SIRT1, which facilitated deacetylation and interaction of PPAR-γ and PRDM-16, hence inducing BAT activation (122). In humans, capsaicin prevented weight gain and maintenance by an increase in resting energy expenditure and fat oxidation (123–125). Meta-analyses of human studies have identified capsaicin as an anti-obesity agent (126,127).

Capsaicin's pungency may limit its clinical use in food. A potential alternative to capsaicin is the use of capsinoids, the non-pungent capsaicin analogues that are equally potent at enhancing thermogenesis, promoting brite adipocyte biogenesis, fat oxidation and lipolysis, sympathetic nerve activity and weight reduction in both rodents and humans (126,128–138). Capsinoids act synergistically with cold temperature and additively with exercise to enhance energy expenditure, brite adipocyte biogenesis and activity (135,136). Capsinoids enhanced energy expenditure in wild-type mice but not in TRPV1 knockout mice or chemical TRPV1 blockade, suggesting the involvement of gastrointestinal TRPV1 (129,139). The gastrointestinal TRPV1/sympathetic nervous system/β_2-adrenoceptor axis has been proposed as a novel approach to biogenesis of brite adipocytes using fish oil and capsinoids (136,140,141). The capsinoid, dihydrocapsiate, is found in a few plant species at typically low abundance but can be synthesised (142). In mice, dihydrocapsiate (0.1 % in food) prevented diet-induced increase in weight gain (143). Another capsaicin analogue, nonivamide, showed weight gain prevention and increased peripheral serotonin release in humans with moderate overweight (144,145). Also, *in vitro* conditions using different cell lines (3T3-L1, Caco-2 and SH-SY5Y cells) have shown that nonivamide inhibited adipogenesis and enhanced energy expenditure ability (146–148). However, clinical trials studying dihydrocapsiate supplementation produced less convincing results than rodent studies (149,150). Chemically

synthesised dihydrocapsiate received GRAS status from the US-FDA (151).

Other dietary constituents showed TRPV1-dependent anti-obesity effects. 6-Paradol from ginger increased energy metabolism in BAT and increased expression of UCP1 by the activation of sympathetic nerve activity (143). KetoA [10-oxo-12(*Z*)-octadecenoic acid], a linoleic acid metabolite, is produced by gut lactic acid bacteria and hence can provide an important link for gut-brain axis in metabolism and energy regulation (152). KetoA activated TRPV1 using calcium imaging and whole patch clamp methods and enhanced adrenaline turnover in adipose tissues (152). Dietary intake of KetoA enhanced energy expenditure (browning) in normal mice, thereby protecting mice from diet-induced obesity, but not in TRPV1-deficient mice (152). Oleuropein, an agonist of both TRPV1 and TRPA1, enhanced UCP1 expression in BAT with a concomitant decrease in the visceral fat mass of high-fat diet-fed obese rats through enhanced noradrenaline secretion via β-adrenergic action following TRPA1 and TRPV1 activation (153).

Body-weight gain increased colonisation of harmful bacterial populations and increased lipopolysaccharide production (metabolic endotoxaemia) (154,155). The anti-obesity effect of capsaicin may involve an improved gut microbiota in rodents and humans fed with high-fat diet. Capsaicin increased the Firmicutes/Bacteroidetes ratio (156,157), decreased Proteobacteria (158), increased *Faecalibacterium* abundance (157), increased *Akkermansia muciniphila*, a mucin-degrading bacterium (158), increased butyrate-producing *Ruminococcaceae* and *Lachnospiraceae* (159), decreased the lipopolysaccharide-producing family S24_7 (159), increased *Roseburia* (156), decreased *Bacteroides* and *Parabacteroides* (156) and increased health-promoting gut bacteria including *Lactobacillus* sp., *Bifidobacteria sp*. and *Akkermensia muciniphila* (117). Predicted function analysis showed depletion of genes involved in bacterial lipopolysaccharide synthesis in response to capsaicin, hence countering metabolic endotoxaemia (159). Capsaicin directly upregulated expression of mucin 2 gene (*Muc2)* and antimicrobial protein gene, *Reg3g*, in the intestine (158). In germ-free mice, faecal microbiota transplantation experiments demonstrated that dietary capsaicin-induced protection against high-fat diet-induced obesity is transferrable (159). In humans, dietary capsaicin-induced gut beneficial effects were only seen in Bacteroides enterotype and not in Prevotella enterotype (157). Hence, the beneficial effects of dietary capsaicin on energy homeostasis are associated with relevant alterations in gut microbial populations. Also, the enhanced production of L-lactate by *Lactobacillus acidophilus* in the presence of red chili or capsaicin is due to increased metabolic activity (160), which suggests that capsaicin enhanced fermentation activity of bacteria. There is a high likelihood of a direct link between capsaicin actions on gut microbiota and TRPV1 expression and function in the gastrointestinal tract, given the sensory nature of TRPV1 and increased crosstalk between gut and brain, but this is still not proved.

Transient receptor potential vanilloid 1 is co-expressed and co-localised with calcitonin gene-related peptide (CGRP) and TRPV1 activation released CGRP (161,162). CGRP induced anorexia and energy expenditure by stimulating anorexigenic neuropeptide and/or inhibiting orexigenic neuropeptide expression (163), yet CGRP has been associated with development of insulin resistance (164). CGRP also induces energy expenditure, increasing the skin temperature and BAT tissue thermogenesis, while CGRP-positive sensory innervations in adipose tissue convey information on peripheral lipid stores to the brain to modulate adipokine secretion (163). Male mice lacking CGRP receptors were protected from obesity induced by high-fat diet, and CGRP regulated the content of lipid in liver, muscle and adipose tissue (165). Long-term use of high-fat, high-carbohydrate diet sensitised TRPV1-mediated vascular reactions and CGRP release, which are relevant to the enhanced headache susceptibility of individuals with obesity (166). However, the exact role and second messenger signalling following CGRP release is still not clear, but the TRPV1-CGRP association might play a role in TRPV1-induced metabolic effects.

Several lines of evidence suggest TRPV1 blockade as a therapeutic approach for weight control. TRPV1-null mice with no functional TRPV1 signalling when fed a high-fat diet accumulated less abdominal and subcutaneous fat as a result of higher thermogenic capacity compared with their wild-type counterparts (167). Further, TRPV1 desensitisation may play a critical role in the treatment of obesity (30). Desensitisation of the capsaicin-sensitive afferent abdominal fibre enhanced weight loss in rats by attenuating hypometabolic adaptation to food deprivation (168). Likewise, reduction in weight gain and body fat contents have been observed in diet-induced obese rats following vagotomy or capsaicin-mediated deafferentiation (169). Supporting these studies, improvement in obesity-induced glucose tolerance, hypertension and low-grade inflammation was observed in high-fat diet-fed TRPV1 knockout but not in high-fat diet-fed wild-type mice (170). Further, TRPV1 knockout mice showed an extended lifespan and better metabolic profile in old age by CRTC1/CREB signalling (171).

Transient receptor potential vanilloid 1 agonists exert complex pharmacological effects, initially producing activation followed by a long-lasting desensitisation suggesting that this mechanism for inhibition of TRPV1 is important for the chronic pharmacological effects of TRPV1 agonists (167). TRPV1 desensitisation is important in the chronic metabolic actions of capsaicin as a TRPV1 agonist; the logical extension of this concept is that selective antagonists for this receptor may also play an important role in control of

metabolic activity (172). In addition, TRPV1 agonists cause both desensitisation and ablation of the neurons expressing TRPV1, thus producing higher efficacy. However, antagonists only block TRPV1 sensitisation of neuronal excitation (172). Three methods for chronically decreased TRPV1 responses have been suggested – selective disruption of the TRPV1 gene, destruction of sensory neurons that express TRPV1 and pharmacological activation/desensitisation of TRPV1 (167). We have listed the different mechanisms of actions for TRPV1 agonists (agonism or desensitisation) and antagonists in Table 1.

Transient receptor potential vanilloid 2 channels

Transient receptor potential vanilloid 2, a non-selective calcium-permeable cation channel, cloned as an analogue of TRPV1, is activated by noxious heat with an activation threshold >52°C, as well as by mechanical stimuli and many endogenous lipid mediators (186). It is present in neuronal and non-neuronal cell types and is involved in many physiological functions (186). TRPV2 was abundantly expressed in pre-adipocytes (187,188), differentiated adipocytes (188) and both murine brown and WAT (189). TRPV2 mRNA expression levels in BAT and subcutaneous WAT were increased in high-fat diet-induced obese mice and *db*/*db* mice (190). Moreover, the expression of TRPV2 was increased in differentiated brown adipocytes compared with pre-adipocytes at mRNA, protein and functional levels (191).

Two reports in 2016 established the novel role of TRPV2 in BAT differentiation, browning-induced thermogenesis and enhanced energy expenditure (191,192). The expression of thermogenic genes, *UCP1* and *PGC1-α*, was lower in brown adipocytes isolated from TRPV2 knockout mice compared with wild-type mice (191). TRPV2 activation was associated with inhibition of BAT differentiation whereas its knockdown facilitated differentiation (191). Further, BAT activation-induced thermogenesis and brite phenotype were increased by TRPV2-mediated calcium influx (192). TRPV2 knockout mice were prone to obesity

Table 1 Summary of TRPV1-modulating different mechanisms (agonism, antagonism, knockout and desensitisation)

Modulation	Mechanism	Effects	Comments
Capsaicin (agonist)	Sensory TRPV1 agonism	Energy expenditure, appetite suppressive effect (173)	Effective in capsaicin non-user humans
		Increased respiratory quotient (173)	Orally consumed capsaicin but not from capsaicin capsules in humans
	TRPV1 agonism	Carbohydrate oxidation and increased plasma adrenaline and noradrenaline (174)	Long distance male runners
		Increased energy expenditure and increased plasma adrenaline and noradrenaline (175)	Humans
TRPV1 knockout	TRPV1 knockout	High locomotor activity while young but become hypoactive upon ageing for 61 weeks, weight was lower while young but become obese upon ageing for 61 weeks (176)	TRPV1 knockout mice
		Reduced locomotor activity, more leptin-resistant and insulin-resistant (120)	TRPV1 knockout mice fed with high-fat diet
		Gained less weight as compared with wild type in 11% fat diet (167)	TRPV1 knockout mice
Capsaicin (agonist)	TRPV1 desensitisation	Impaired exercise endurance in treadmill running (177)	Neonatal capsaicin deafferentation in Sprague Dawley rats
		Impairment in the elevation of plasma adrenaline and noradrenaline after exercise due to depletion of substance P in C-fibers (178)	Neonatal capsaicin-treated Sprague Dawley rats
		Prevented the development of spontaneous hyperglycaemia (179)	Zucker diabetic fatty rats
		Improves oral glucose tolerance (180)	Obese Zucker rats
		Increases *in vivo* insulin sensitivity, skeletal muscle glycogen synthesis, reduction of glucagon, corticosterone, adrenaline and noradrenaline hormones in plasma (181)	Rats
Resiniferatoxin (agonist)	TRPV1 desensitisation	Improves glucose tolerance and increases insulin secretion (182)	Zucker diabetic fatty rats
		Improves insulin sensitivity (183)	Male obese Zucker rats
BCTC (antagonist)	TRPV1 antagonist	Decreased hyperglycaemia, hypertriglyceridaemia, enhanced glucose clearance in OGTT and insulin secretion (184)	Hyperinsulinaemic *ob*/*ob* mice
AZV1 (antagonist)		Enhanced insulin sensitivity (185)	*ob*/*ob* mice

and showed insulin resistance after high-fat diet administration (192). Hence, these two studies from the same group have contradictory results with one suggesting TRPV2 to be responsible for inhibition of BAT differentiation and the other one suggesting TRPV2 to be involved in thermogenesis through BAT activation (191,192). A possible explanation is that TRPV2 has different mechanisms of action at different stages of adipocyte differentiation where it may inhibit differentiation of BAT at initial stages and promote it at later stages. Probenecid (TRPV2 agonist), 2-aminoethoxydiphenyl borate (TRPV1-3 agonist) and an increase in extracellular temperature from 25 to 42°C caused TRPV2-dependent increases in intracellular calcium in adipocytes (187,188). This was blocked by ruthenium red, a non-selective antagonist. Further, silencing of TRPV2 inhibited cyclin D1, cyclin E and p-ERK1/2 and decreased adipocyte cell proliferation by reducing p-Akt kinase (187). These results suggest that activation of TRPV2 could be an intriguing therapeutic approach for the treatment and prevention of obesity in humans.

Transient receptor potential vanilloid 3 channels

Transient receptor potential vanilloid 3 channels, highly homologous to TRPV1, have a calcium/sodium permeability ratio of ~10 and are expressed in skin and hair follicles (193). Expression of TRPV3, although lower than other TRP channels, is found in other tissues including tongue, brain, testis, colon and cornea (194,195). TRPV3 is also expressed in discrete brain regions and primary sensory afferents (193,196) including primary vagal afferents (197,198). TRPV3 mRNA expression levels were decreased in subcutaneous WAT and inducible BAT of high-fat diet-induced obese, *ob*/*ob* (leptin-deficient) and *db*/*db* (leptin receptor-deficient) mice (190,199). TRPV3 receptors were also observed in 3T3-L1 adipocytes (199). TRPV3 is one of the thermo-TRPs and is activated in the physiological temperature range from 22 to 40°C (194,195). Defective responses to innocuous and noxious heat were observed in TRPV3 knockout mice (200). However, the TRPV3 agonists, thymol and ethyl vanillin, did not induce thermogenesis and heat diffusion at physiological temperatures (201).

High-fat diet feeding decreased the expression of proopiomelanocortin (POMC) gene, an anorectic gene in hypoglossal nucleus and medial nucleus tractus solitarius of obesity-prone rats, which was positively correlated with increase in food intake, body-weight gain, mean arterial blood pressure and increased TRPV3 expression in these regions (202). Infrared (heat) treatment as a stimulus for TRPV3 reduced food intake and decreased the number of TRPV3-positive neurons (202). Activation of TRPV3 suppressed adipocyte differentiation (199). The TRPV3 agonists, catechin and epicatechin, prevented adipogenesis by inhibiting the phosphorylation of insulin receptor substrate 1, the downstream phosphoinositide 3-kinase/Akt/forkhead box protein O1 axis and the expression of the adipogenic genes *PPAR-γ* and *C/EBP-α* (199). TRPV3 overexpression limited adipogenesis in the 3T3-L1 cells (199). Chronic treatment with TRPV3 activators prevented high-fat diet-induced weight gain (199). Essential oils such as carvacrol, eugenol and thymol as major components of plants including oregano, savory, clove and thyme are TRPV3 activators (203). The activity of these compounds, along with novel TRPV3 agonists such as catechin and epicatechin, which are part of our daily dietary and food habits, allows us to hypothesise that foods containing these compounds will reduce obesity.

Transient receptor potential vanilloid 4 channels

Transient receptor potential vanilloid 4, a close family member of TRPV1, is a sensor of osmolarity (204,205), temperature (206,207) and endogenous lipids (208). TRPV4 is expressed in both excitable and non-excitable tissues such as the kidney, lung, brain, dorsal root ganglia, bladder, fat, testis, liver, heart, skin, airway smooth muscle cells, vascular endothelium, chondrocytes and osteoclasts (209–215). *TRPV4* mRNA expression has been shown in the peripheral sensory ganglia and osmoregulation-related brain structures including lamina terminalis and hypothalamic median preoptic region (204). The high expression of *TRPV4* gene in the hypothalamus, a brain area that regulates neuronal influence on satiety and hunger, suggests its role in energy expenditure and weight regulation. This is supported by the expression and function of TRPV4 channels in cultured adipocytes from humans (216). TRPV4 is also present in bovine articular chondrocytes and is regulated by obesity-driven metabolic mediators (217), suggesting its role in crosstalk between obesity and other complications. TRPV4, a thermo-TRP, is important for the maintenance of core body temperature, which is a well-known metabolic characteristic of mammals (214).

Transient receptor potential vanilloid $4^{-/-}$ mice did not show any difference in weight gain compared with wild-type mice on normal rodent diet. However, high-fat diet feeding in $TRPV4^{-/-}$ mice produced no body-weight gain or obesity phenotype in both male and female mice (218). Moreover, $TRPV4^{-/-}$ mice displayed an increased energy expenditure including gene expression related to energy expenditure and oxygen consumption rate, as well as decreased serum leptin concentrations (218). The possible reasons include that deletion or inactivation of TRPV4 induced compensatory increases in other TRP channels such as TRPC3 and TRPC6 and elevation of calcineurin activity increasing fuel oxidation in skeletal muscle, hence an increase in energy expenditure and protection from diet-induced obesity in mice (218). $TRPV4^{-/-}$ mice showed

protection from diet-induced obesity and insulin resistance, with increased browning of visceral adipose tissue by an increase in expression of *UCP1* and its downstream mediators, *PGC1-α* expression, mitochondrial biogenesis and oxidative metabolism (219). Knockdown of TRPV4 using shRNA technology resulted in an increase in total respiration in knockdown adipocytes indicating an increased capacity for energy expenditure (219). Further, TRPV4 has a pro-inflammatory effect on adipose tissue (219). However, in another study, $TRPV4^{-/-}$ mice developed more severe diet-induced obesity (weight gain and increase in adipocyte size) and increased knee osteoarthritis scores after high-fat diet feeding (220). Alteration of TRPV4 protein expression after high-fat diet administration is adipose tissue depot-selective (221). There was no difference in epididymal adipose tissue in control and high-fat diet groups, whereas in subcutaneous adipose tissue, high-fat diet elevated TRPV4 protein expression (221). Irisin, an exercise-induced myokine, induced endothelium-dependent vasodilatation through stimulation of extracellular Ca^{2+} influx via TRPV4 channels in rat mesenteric arteries (222).

In children, maternal obesity is a risk factor for obesity (223). There are limited studies on the molecular mechanisms, and hence, effective preventive strategies are limited. TRPV4 has been studied as an important molecular marker, and selective TRPV4-based interventions can prevent long-term adverse metabolic effects of maternal high-fat nutrition (224). The offspring of high-fat diet-consuming mothers showed a sixfold increase in *Trpv4* mRNA expression, which was prevented in an intervention group (lactation) (224). Also, WAT adipokine/cytokine release and metabolic gene/protein expression were returned to control levels in TRPV4-based intervention groups (224). Also, in humans, population-based TRPV4 genotyping studies suggested that body mass index and obesity correlate with TRPV4 genotypes in Taiwanese people (225). Also, obesity status using Asian and National Institute of Health criteria was associated with TRPV4 genotypes (225). Overall, these studies have demonstrated that TRPV4 could be a candidate gene for targeting obesity in rodents as well as in humans, deserving further evaluation if selective agonists and antagonists can be developed.

Transient receptor potential ankyrin 1 channels

The TRPA1 channel, cloned in 1999 (226), is a molecular sensor of noxious cold temperature and also a sensor for the irritation-causing chemicals in mustard oil, tear gas, environmental pollutants and tobacco products (227). TRPA1 is expressed in many tissues and cell types (228–241). It is functionally expressed in the brain stem, adipose tissue, sensory nerves innervating different peripheral tissues, gastrointestinal tract and pancreas (228,234–236,242–244).

Transient receptor potential ankyrin 1 agonists such as allyl isothiocyanate, cinnamaldehyde and methyl syringate reduced the food intake by modulation of gastric emptying and gut hormone secretion (245,246). This decrease in gastric emptying was inhibited in the presence of the non-selective TRP channel blocker (ruthenium red), tryptophan 5-hydroxylase inhibitor (p-chlorophenylalanine) or 5-HT_3 receptor antagonist (granisetron) (245). The TRPA1 agonist, methyl syringate, inhibited gastric emptying and cumulative food intake and increased anorectic gut hormone polypeptide YY, with the effect prevented by the non-selective TRP channel blocker, ruthenium red, or the TRPA1 selective blocker, HC-030031, in mice (246). High-fat diet-induced alterations in leptin and ghrelin release were prevented by cinnamaldehyde administration (247). The presence of TRPA1 in stomach with co-expression of ghrelin on secretory cells of mouse and its activation *via* cinnamaldehyde decreased the secretion of ghrelin in TRPA1-dependent manner, which was blocked by the TRPA1 antagonist, HC-030031 (243). TRPA1 channels are present in intestinal enteroendocrine L-cells, activation of which induced TRPA1-dependent increases in GLP-1 secretion (248). TRPA1 activation by allyl isothiocyanate, carvacrol or polyunsaturated fatty acids induced GLP-1 secretion in TRPA1-expressing primary murine intestinal cultures and GLUTag, a murine enteroendocrine cell line that expresses proglucagon. The response was not shown in cultured cell lines from $TRPA1^{-/-}$ mice or after pharmacological blockade of TRPA1 receptors (248). TRPA1 was co-expressed with cholecystokinin, serotonin and ghrelin-producing cells and regulated the secretion of these hormones (249). TRPA1 agonists, allyl isothiocyanate and cinnamaldehyde increased serotonin release from enteroendocrine L-cells (235). The expression of TRPA1 has also been found in duodenal mucosa from mice and humans and in intestinal mouse neuroendocrine STC-1 cells, which, upon activation, induced TRPA1-dependent increases in cholecystokinin secretion (234,250). Cinnamaldehyde supplementation prevented fasting-induced hyperphagia, lipid accumulation and inflammation in diet-induced obese animals (247,251).

Expression of TRPA1 has also been observed in pancreatic β-cells, with activation inducing insulin release in TRPA1-dependent manner (242). TRPA1 agonists regulated autonomic thermoregulation (201) and thermogenesis in BAT (252) in mice and rats, respectively. Also, TRPA1 is involved in enhanced headache susceptibility in individuals with obesity (253). Overall, these studies have established a role for TRPA1 in control of weight gain, hormone secretion, thermogenesis, neuronal function, nutrient sensing and pancreatic function, which suggests a potential therapeutic role of these channels in metabolic syndrome.

Transient receptor potential melastatin 2 channels

Transient receptor potential melastatin 2 channels are expressed in the skin, brain, pancreas, spleen, kidney and immunocytes, including lymphocytes, neutrophils and monocytes/macrophages, and are involved in calcium signalling in these tissues (254–256). TRPM2 is activated by warm temperature, increased reactive oxygen species (oxidative stress), intracellular endogenous ligands, such as ADP-ribose and cyclic ADP-ribose, and pyridine dinucleotides including NAD, NAAD and NAADP (257–259). TRPM2 deletion protected mice from developing diet-induced obesity and insulin resistance. TRPM2-null mice showed higher energy expenditure, enhanced insulin sensitivity, anti-inflammatory effects both systemic and tissue-selective (adipose tissue and liver), increased levels of PPAR-α (lipid metabolic marker) and PGC1-α (browning marker) in WAT hence a phenotype with less body mass and adiposity (260). TRPM2 has a key role in thermoregulation as a mediator for thermosensation on skin and its integration in higher brain centres. Warm temperature detection is related to vascular dilatation with thermogenesis modulation in peripheral organs such as BAT and skeletal muscle, and TRPM2 might play a role in integration of temperature-sensing information and accordingly modulate the response to various metabolic states, which includes obesity (261). Therefore, TRPM2 could integrate the information and modulate physiological functions in response to systemic metabolic states. Understanding the machinery of TRPM2-mediated regulation of physiological functions could provide novel strategies to control pathological situations involving metabolic changes.

Transient receptor potential melastatin 5 channels

Transient receptor potential melastatin 5 channels are non-selective monovalent cation channels activated by increases of intracellular calcium (262,263). TRPM5 is highly expressed in liver but also present in other tissues including the heart, brain (frontal cortex, spinal cord and pituitary gland), kidney, spleen, lung, testes, stomach, intestine, prostate and pancreas (islets of Langerhans) (264–267). Further, using a genetic model (TRPM5-*Cre* reporter mouse), TRPM5 expression was shown in taste bud cells and olfactory epithelium (268).

Treatment with the TRPM5 inhibitor, quinine, prevented high-fat diet-induced weight gain in wild-type animals, but the mechanisms were not completely TRPM5-dependent as the same effect was observed in TRPM5$^{-/-}$ mice (269,270). Further studies concluded that TRPM5$^{-/-}$ mice are resistant to the development of obesity (271,272). However, the caloric intake in TRPM5$^{-/-}$ was lower suggesting that its presence on taste buds might play a role and that TRPM5 is not directly involved in weight gain (271,272). Thus, it can be hypothesised that TRPM5-dependent sweet taste may be responsible for overeating in wild animals resulting in high caloric intake and glucose intolerance (273). Wild-type and TRPM5$^{-/-}$ mice, when administered high-fat diets, if they consume the same calories, will have similar weight gain (273), which underlies the hypothesis that lower caloric intake due to loss of taste perception is responsible for the obesity-resistant phenotype of TRPM5$^{-/-}$ animals. With the role of TRPM5 in taste perception for sweet, bitter and umami, it may become a natural target for the development of preventive or therapeutic strategies for controlling energy intake and hence weight gain (274).

Transient receptor potential melastatin 8 channels

The TRP cation channel subfamily M member 8 (TRPM8), also known as the cold and menthol receptor and the most significant of TRPM series, is an ion channel that acts as a cold transducer in the sensory system and enables mammals to detect and avoid environmental cold. The channel opens when temperature drops below 25°C and remains open at low temperatures (275–277). Genetically engineered mice that lack the TRPM8 receptor have reduced cold aversion and defective responses to cooling agents, including menthol but also icilin and eucalyptol, which is why the crucial contribution of TRPM8 to cold temperature and cold mimetic sensing in mammals is widely accepted (275–277). TRPM8 receptors are highly enriched in the membranes of two subsets of sensory neurons – thermoreceptors responding to graded cool and cold stimuli, which allow the direct encoding of environmental cool, and nociceptors responding to deep, painful cold and re-enforcing cold aversion and protective behaviours (278). Sensory nerve endings with TRPM8 not only are present in the skin but also innervate mucous membranes including the entire intestinal tract (279–281) and thereby are involved in core body temperature detection and regulation (Fig. 2) (282). TRPM8 is widely expressed in different sensory and non-sensory tissues (265,280,281,283–288) including metabolically active tissues such as adipose tissues (189,289–291) and brain (hypothalamus) (292), and it is modulated by exogenous agonists and antagonists including menthol (276).

Exposure of cold temperature and subsequent increases in whole-body thermogenesis are related. The mechanism of cold-induced thermogenesis mainly involves activation of the sympathetic nervous system and is termed as adaptive thermogenesis (293,294). It is mainly divided into shivering and non-shivering thermogenesis, involving skeletal muscle and adipose tissue, respectively. TRPM8 is an important sensor that helps in maintaining body temperature (295). Topical menthol application to the skin of whole trunk in mice, mimicking *in vivo* cold exposure, led to an increase in core body temperature, which was positively correlated with expression of UCP1, an essential thermogenic protein

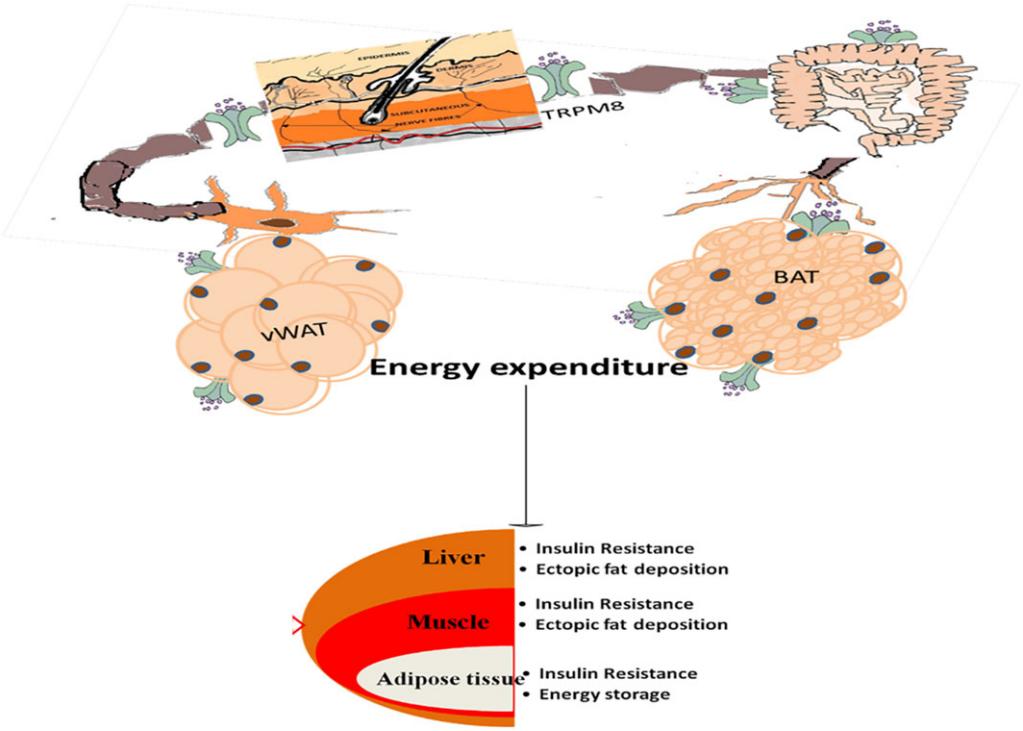

Figure 2 Schematic diagram presenting mechanism of action of TRPM8 agonists in preventing obesity via enhancing energy expenditure. TRPM8 activation at sensory nerve ending (on skin and gut) induced adaptive thermogenesis, which lead to the induction of energy expenditure via different mechanisms. These effects pharmacologically mimic cold condition and prevent high-fat diet-induced insulin resistance, ectopic fat deposition and weight gain. BAT, brown adipose tissue; TRPM, transient receptor potential melastatin; WAT, white adipose tissue. [Colour figure can be viewed at wileyonlinelibrary.com]

in BAT, which mediates mitochondrial uncoupling and leads to weight gain when deficient, as demonstrated in UCP1-knockout mice (295,296). TRPM8-deficient mice displayed an increase in tail heat loss and lower core body temperature when housed in a mild cold environment. This can be associated to the development of late-onset obesity with glucose and lipid metabolic dysfunction, diurnal hyperphagia and reduced fat oxidation in TRPM8-deficient mice (297). Non-shivering thermogenesis is crucial for mammals as a defence mechanism against cold and classically involves adrenergic afferent activation (298). However, the involvement of TRPM8 in BAT with dietary administration of menthol increasing UCP1 expression indicated a novel pathway for UCP1-induced thermogenesis, without involvement of β-adrenergic signalling, that reversed diet-induced obesity in wild-type but not in TRPM8$^{-/-}$ mice (289). The fat cells can directly sense the cold temperature and activate the thermogenic machinery of the adipose tissue (299). Activation of TRPM8 using menthol or icilin *in vitro* increased UCP1 expression, glucose uptake, heat production and ultimately the induction of brite-like phenotype in WAT (290,291). Intragastric administration of the TRPM8 agonists, menthol and 1,8-cineole, increased colonic and BAT temperature (201). Involvement of TRPM8 thermogenesis as a defence mechanism against cooling has also been evident in anaesthetised rats where application of menthol to the trunk before slow (0.005^0C/s) or rapid (0.1^0C/s) cooling of ambient temperature increased oxygen consumption, decreased respiratory coefficient and increased vasoconstrictive response of cooling (300,301). It is clear that TRPM8 is critical for maintenance of core body temperature, at least in cold conditions, and TRPM8 agonists transiently increase body temperature. The administration of TRPM8 antagonists in rat and mice implanted with radio telemetry probes decreased body temperatures (302). Importantly, TRPM8 is also present on WAT in humans (Fig. 2) (290). Thus, identification of novel non-adrenergic targets related to cold activation should allow the activation of thermogenesis and in turn increase energy expenditure but also have limited adverse effects associated with sympathetic activation.

Transient receptor potential canonical channels

Transient receptor potential canonical channels in neurons and adipocytes regulate energy homeostasis (303–305). POMC-expressing arcuate nucleus neurons express TRPC 1, 4 and 5 in mice (305). TRPC1 and TRPC5 channels have differential functional expression during adipocyte differentiation with mRNA levels increased 16 and 37-fold,

respectively (306). Also, both these TRP subunits were identified in fat from mice and humans (306).

Transient receptor potential canonical channels as a heteromer of TRPC 1, 4 and 5 channels regulate leptin-dependent depolarisation and activation of hypothalamic POMC neurons by a Janus 2 tyrosine kinase (Jak 2)/phosphatidylinositide 3-kinase/phospholipase Cγ1 pathway (305). TRPC (TRPC5 and TRPC1) channels also regulate serotonin-mediated depolarisation in a different set of POMC neurons (leptin-insensitive but express 5-HT_{2C} receptors) (307). Neuronal and POMC-specific loss of TRPC5 subunits was sufficient to decrease energy expenditure and increase food intake resulting in elevated body weight (308). TRPC5-deficient POMC neurons also prevented the anorexigenic effects of leptin and 5-HT_{2C} receptor agonists and the 5-HT_{2C} receptor agonist lorcaserin-induced improvements in glucose and insulin tolerance (308). Whole-body and mediobasal (direct detection of metabolic signal) hypothalamus TRPC3-deficient mice have increased body weight and food intake, implicating the involvement of TRPC3 in hypothalamic glucose detection and energy regulation (309). TRPC3-deficient mice abolished increased insulin secretion following intra-carotid glucose injection as well as intracerebroventricular glucose injection-induced anorectic effects (309). Loss of function of TRPC3 prevented calcium responses to glucose in mediobasal hypothalamic neurons (309).

Adiponectin release was increased by disruption of TRPC1/TRPC5 in adipocytes *in vitro* with blocking antibodies or small inhibitory RNA or *in vivo* by overexpression in mice of a dominant negative TRPC5 protein (306). TRPC1 functions as a major Ca^{2+} entry channel in adipocytes. TRPC1 knockout mice have lower fat mass and fasting glucose concentrations when fed high-fat diet and exercised as compared with littermate control mice (310). Adipocyte numbers (subcutaneous and visceral adipose tissue) and autophagy markers were decreased whereas apoptosis markers were increased in both TRPC1 knockout mice fed a high-fat diet and exercised, hence suggesting important roles of TRPC1 in the regulation of adiposity (310). Polyunsaturated fatty acids such as α-linolenic acid, docosahexaenoic acid and eicosapentaenoic acid are inhibitors of TRPC1/C5 suggesting the involvement of these channels in metabolic benefits of these fatty acids (306).

Others

Additional TRP channels have been noted to be involved in obesity. Ten thermo-TRPs are expressed in both inducible BAT and subcutaneous WAT in mice (311). TRPV6 and TRPC6 showed differential expression in murine WAT and BAT, suggesting differential roles in energy expenditure and adaptive thermogenesis (189). TRPC4 and TRPC6 were differentially expressed in pre-adipocytes and adipocytes suggesting their importance during adipogenesis (189). Population-wide genetic linkage analysis implicated TRPC4 (312), TRPML (313) and TRPP2 (313) in humans with obesity. Expression of TRPC1, TRPC3, TRPM2, TRPM5, TRPV4, TRPV5, TRPV6, MCOLN2 (TRPML2) and MCOLN3 (TRPML3) genes was decreased whereas gene expression of TRPC6 was increased in a Turkish population with metabolic syndrome, hence suggesting a relationship between gene expression of TRP channels and metabolic syndrome (314). The presence of many TRP channels could be causal for metabolic function but could be casual given the many physiological functions of these channels. More in-depth animal studies using knockout models followed by population-based clinical studies will unravel the involvement of these channels in the pathogenesis and prevention of obesity.

Expression of transient receptor potential channels in other metabolically active tissues (pancreas and skeletal muscle) and their sensory nervous innervations

Pancreas and skeletal muscles are metabolically active tissues. The expression of TRP channels was observed in different pancreatic cell lines (β TC-3 [TRPC4, TRPC6 but no TRPC1]; INS-1 [TRPC1, TRPC4, TRPM3, TRPM5 and TRPV1]; MIN6 [TRPC1, TRPM5, TRPV2 and TRPV4]), mouse pancreatic islets (TRPC1, TRPC4, TRPM2, TRPM3, TRPM4, TRPM5, TRPV2 and TRPV4), rat pancreatic islets (TRPA1, TRPC1, TRPC4, TRPM2, TRPV1 and TRPV5) and human pancreatic islets (TRPC1, TRPM2, TRPM4, TRPM5, TRPV5 and TRPV6) (242,315–320). RNA sequencing data of purified pancreatic β-cells suggested that TRPM7, TRPP2, TRPM4, MCOLN1 (TRPML1), MCOLN3 (TRPML3), TRPC1, TRPM3 and TRPM2 are expressed, while the remaining TRP channels are not expressed or have very low expression in the β-cells from humans (321). Mild heat exposure induced TRPM2-dependent and ATP-sensitive K channel-independent cytosolic Ca^{2+} increase and insulin release in pancreatic islets and in rat insulinoma RIN-5F cells lines (258). Further, secretion of insulin from pancreatic islets of TRPM2 knockout mice was impaired in response to glucose (322). TRPM2 knockout mice also exhibited impaired oral and intraperitoneal glucose tolerance test (322). Similarly, TRPM3 channel activators, pregnenolone sulphate and CIM0216, also increased the insulin secretion from pancreatic β-cells *in vitro* (323,324). Likewise, the knockdown of TRPV2 from MIN6 or presence of tranilast, a TRPV2 antagonist, inhibited the release of glucose-induced insulin secretion *in vitro* (325). Osmotic, thermal or pharmacological activators of TRPV4 increased insulin secretion in INS-E1 β-cells *in vitro* (326). TRPM7 and TRPC3 are dominant TRP

channels in mouse skeletal muscles among many other TRP channels including TRPM7, TRPC3, TRPV3, TRPC1, TRPC4, TRPC6, TRPM4, TRPV6, TRPM2, TRPC2, TRPC3, TRPV2, TRPV3, TRPV4, TRPM5, TRPM3, TRPM2, TRPM3, TRPM6, TRPM7 and TRPM1 (218,327,328). The expression of these different TRP channels is not uniform in different skeletal muscles (327). Similarly, human skeletal muscles also contain TRPC1, TRPC2, TRPC4, TRPC6, TRPM2, TRPM3, TRPM4, TRPM6 and TRPM7 (218,265,329). The presence of TRP channels in these metabolically active tissues suggests their relevance in metabolism and energy regulation.

Sensory nervous innervations in metabolically active tissues are critical for metabolic homeostasis. WAT contains small diameter, unmyelinated TRPV1-expressing sensory nerves (102). It has been postulated that in the absence of TRPV1-containing sensory nerves, the central control of sympathetic activity in general and lipolysis *per se* was lost;

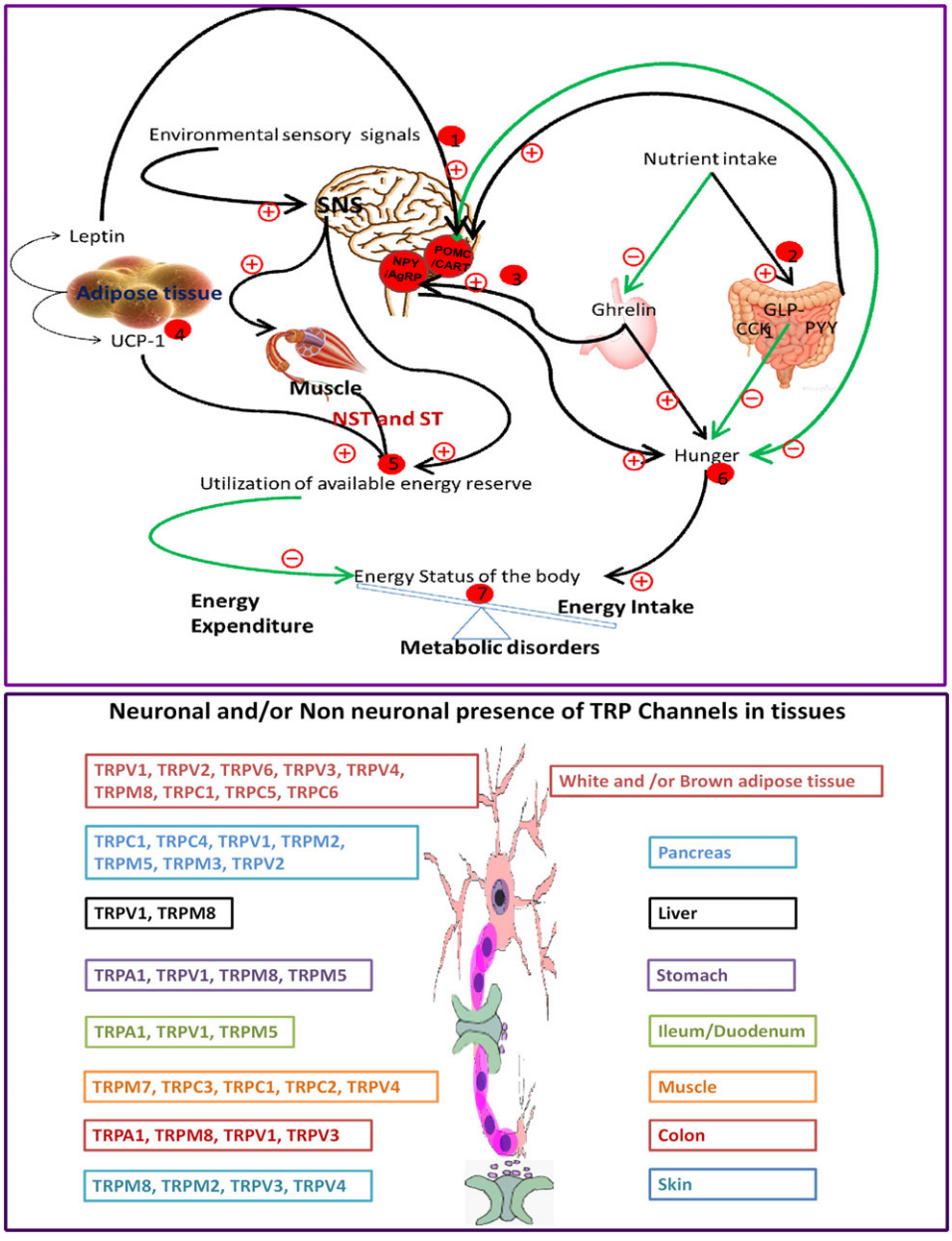

Figure 3 TRP channels can modulate energy regulation by different mechanisms. (1) Modulation of anorectic/orexogenic gene expression; (2) nutrient sensing and modulation of gut hormone and microbiota; (3) modulation of gut-brain axis; (4) adipocyte differentiation modulation; (5) enhanced use of energy stores; (6) regulation of peripheral mechanisms of hunger and satiety; (7) enhanced energy expenditure. TRP, transient receptor potential; TRPA, TRP ankyrin; TRPM, TRP melastatin; TRPV, TRP vanilloid. [Colour figure can be viewed at wileyonlinelibrary.com]

hence, TRPV1-deficient animals showed reduced weight gain as compared with littermate controls (167). CGRP, along with adrenomedullin, is present on sensory nerves (i.e. subpopulation of capsaicin-sensitive A and C primary afferents), isolated preadipocytes and adipocytes, and abdominal fat from humans (330,331). CGRP inhibited noradrenaline-induced thermogenesis in BAT, and this might affect noradrenaline-induced lipolysis in WAT (332). To elucidate this, further electrophysiology-related experiments on WAT and BAT afferents are required. Also, the identification and characterisation of CGRP binding to calcitonin receptor-like receptor and receptor activity modifying protein-1 on sympathetic nerves innervating adipose tissue is important and will enable us to confirm the role of TRP-expressing sensory nerves in adipose tissue-mediated metabolic homeostasis.

Transient receptor potential vanilloid 1 is functionally expressed on sensory nerves innervating the islets and plays a significant role in the development of type 1 diabetes (333,334). It has roles in the regulation of insulin secretion, glucose homeostasis and β-cell physiology, primarily via neuropeptide release (318,333,335). TRPV1/CGRP and TRPM8-expressing sensory afferents innervate the hepatic portal vein and control neuronal regulation of insulin and glucose homeostasis (336). Liver-related paraventricular nucleus neurons are also regulated by TRPV1, suggesting its influence in the regulation of hepatic glucose production (337).

Transient receptor potential vanilloid 1 and TRPA1 modulate pre-autonomic neuronal activity at the level of hypothalamus and brainstem by increasing or decreasing autonomic nervous system activity (244). Increased sympathetic and decreased parasympathetic activity have been associated with development of metabolic syndrome (244). TRPA1 is functionally expressed in many brain areas, including the supraoptic nucleus of the hypothalamus and nucleus tractus solitarii, and is able to modulate neuronal activity, glutamate release and vagal communication (338,339). TRPA1 can be the crucial link between oxidative stress, inflammation, altered neuronal activity and vagal dysfunction, all these playing major roles in metabolic dysregulation (244). TRPM8-sensory fibres innervate the main tail vessels (297). TRPM8-deficient mice induced an increase in tail heat loss when housed at cold temperatures and during food deprivation; hence, TRPM8 is required and is involved in thermoregulation and energy expenditure (297).

Recent advances in the role of gut-brain axis in metabolic complications have also rekindled the discussion on the involvement of TRP-expressing sensory afferents in the gastrointestinal tract (280,340–344). TRPV1 is present is gastrointestinal vagal afferents (340,342,344,345). At high concentrations, capsaicin permanently ablated these sensory neurons, a technique used frequently to study the role of the unmyelinated vagal sensory neurons of the gut (346,347). This, along with other techniques, will enable us to delineate the role of TRP-containing sensory nerves in gastrointestinal tract and their importance in the release of gut hormones, nutrient sensing, glucose and insulin homeostasis, gut microbiota and metabolite changes as all of these are of significance for metabolic health. TRPA1 are functionally expressed in the enteric nervous system throughout the mouse intestine and are involved in the release of gut hormones from different locations (343). TRPA1 are present in duodenal mucosa from mice and humans and neuroendocrine STC-1 cells and induce cholecystokinin release (234). TRPA1-induced alterations in gut hormones secretion showed physiological relevance for decreasing obesity (243,246,248,348). Activation of TRPA1-containing myenteric neurons inhibited spontaneous contractions and transit in intestine (343). TRPM8, alone or co-expressed with TRPV1 and TRPA1, is present on colonic sensory neurons and inhibits their downstream chemosensory and mechanosensory actions (280). TRPM8 is also functionally expressed in oesophageal vagal jugular neurons and has a potential role in esophageal sensory transduction (349).

Overall, determining the unique role of sensory TRP channels on different metabolically active tissues may lead to the development of newer brain-periphery axis-based approaches for maintaining proper metabolism.

Conclusion and future directions

The obesity epidemic is a serious global concern. Obesity is a major risk factor for type-2 diabetes (insulin resistance), dyslipidaemia, hypertension and other cardiovascular complications, certain forms of cancer and osteoarthritis. The pharmacological options for obesity prevention and treatment are still very limited. There is now relevant evidence that TRP channels regulate energy homeostasis by different mechanisms including increases in sympathetic outflow, browning of WAT, BAT activation and biogenesis, adaptive thermogenesis, regulating hunger and satiety by central (hypothalamic neuron activation) and peripheral (gut hormone release) mechanisms and enhancing health-promoting gut microbiota (Fig. 3).

Despite recent studies showing promising results related to involvement of these channels in central and peripheral regulation of energy, the translation to preventive or therapeutic strategies to combat obesity in humans is challenging and uncertain. TRP channels have physiological functions in every tissue type, so the responses to changes in channel function are unlikely to be tissue-selective. However, tissue-selective responses may not be required in obesity as all tissues and organs are likely to be damaged. The role of TRP channels in calcium permeability and intracellular calcium signalling is important for their role in energy

homeostasis. However, calcium has many other physiological functions including muscle excitation, redox homeostasis, cell toxicity and death. Hence, it is essential to characterise tissue or cell-specific functions to a particular TRP channel. It is unclear whether channel activation or inhibition, because of desensitisation or antagonism of these channels, primarily TRPV1, is responsible for these effects. Questions remain on the possible central and peripheral upstream and downstream signalling pathways of these channels. The optimal mode of administration, whether through food (prevention or reversal) or therapeutics (oral or topical), is also not clear. These channels are present on multiple tissues, and their involvement in different physiological actions increases the risk of adverse effects during the treatment of obesity from actions on non-metabolic tissues. Thus, the concept that selected TRP channels can be modulated by dietary constituents is intriguing and worth pursuing. In summary, further research is needed before final conclusions are made, but undoubtedly, TRP channels are potential targets for weight management. Hence, this TR(i)P of discovery is essential for metabolically healthy living.

Conflict of interest statement

No conflict of interest was declared

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