Molecules and Cells

Minireview

Transient Receptor Potential Channels and Metabolism

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https://doi.org/10.14348/molcells.2019.0007
www.molcells.org

Transient receptor potential (TRP) channels are nonselective cationic channels, conserved among flies to humans. Most TRP channels have well known functions in chemosensation, thermosensation, and mechanosensation. In addition to being sensing environmental changes, many TRP channels are also internal sensors that help maintain homeostasis. Recent improvements to analytical methods for genomics and metabolomics allow us to investigate these channels in both mutant animals and humans. In this review, we discuss three aspects of TRP channels, which are their role in metabolism, their functional characteristics, and their role in metabolic syndrome. First, we introduce each TRP channel superfamily and their particular roles in metabolism. Second, we provide evidence for which metabolites TRP channels affect, such as lipids or glucose. Third, we discuss correlations between TRP channels and obesity, diabetes, and mucolipidosis. The cellular metabolism of TRP channels gives us possible therapeutic approaches for an effective prophylaxis of metabolic syndromes.

Keywords: metabolic diseases, metabolism, transient receptor potential channel

INTRODUCTION

Transient receptor potential (TRP) channels are highly conserved transmembrane protein channels present in organisms, ranging from worms to mammals (Venkatachalam and Montell, 2007). These cationic channels were first characterized in the vinegar fly, *Drosophila melanogaster*. While a visual mechanism using forward genetic screening was being studied, a mutant fly showed a transient response to constant light instead of the continuous electroretinogram response recorded in the wild type (Cosens and Manning, 1969). Therefore, the mutant was named as *transient receptor potential* (*trp*). In the beginning, researchers had spent two decades discovering the *trp* locus with the germ-line transformation of the genomic region (Montell and Rubin, 1989). Using a detailed structural permeation property analysis in light-induced current, the TRP channel was confirmed as a six transmembrane domain protein, bearing a structural resemblance to a calcium-permeable cation channel (Montell and Rubin, 1989). This channel system shows structural resemblance with voltage-gated cation channels but largely different in composition of the positively charged amino acid residues which determines voltage sensing (Morita et al., 2007). So far, about 100 *trp* genes have been reported in many animals (Nilius et al., 2007). TRP channels are subdivided into two groups and seven subfamilies: Group 1 includes TRPC (canonical, C1-C7), TRPV (vanilloid, V1-V6), TRPM (melastatin, M1-M8), TRPA (ankyrin, A1), and TRPN (NOMP-like). Group 2 includes TRPP (polycystin, P1-P5) and TRPML (mucolipin, ML1-ML3) (Nilius and Owsianik, 2011).

The ancient TRP channels which are present in protists, chlorophyte algae, choanoflagellates, yeasts, and fungi are primarily involved in chemosensory, thermosensory, or mechanosensory functions (Matsuura et al., 2009; Wu et al.,

Received 20 January, 2019; revised 27 July, 2019; accepted 13 August, 2019; published online 23 August, 2019

eISSN: 0219-1032

2010). Many of these functions are remarkably conserved and can be found in various groups, including protists, worms, flies, and humans (Montell, 2005). TRP channels are involved in diverse physiological functions, ranging from sensation (pheromone signaling, visual, auditory, and taste transduction, nociception, and temperature sensation) to motility (muscle contraction and vaso-motor control). Furthermore, TRP channels are the key participants in the regulation of gut motility, mineral absorption, blood circulation, bladder and airway hypersensitivities, body fluid balance, cell growth, and survival (Nilius et al., 2007; Uchida et al., 2017).

Metabolism and glucose homeostasis are tightly regulated processes (Williams and Elmquist, 2012). The central nervous system (CNS) incorporates both central and peripheral signals for the coordinated control and modulation of food consumption, glucose homeostasis, and energy expenditure. However, *in vivo* study of physiological roles of TRP channels expressed in the CNS is still insufficient. Around 30 TRP channels are documented to be expressed in the digestive system. They are involved in taste, gastrointestinal movement, absorption, secretion, and maintenance of mucosal homeostasis (Holzer, 2011; Lee et al., 2016). Interestingly, involvement of various hormones and neurotransmitters alter the activity of channel system that controls the neuronal functions in the central regulation of metabolism (Brownstein, 1977). Combined studies using mouse genetics, together with neuroanatomical methods and electrophysiological examination, have provided new findings about the roles of various ion channels that modulate neurons associated with metabolism and related disorders (Sohn et al., 2013).

TRP channels are present in various metabolically important tissues. They are widely expressed in the pancreatic cells, liver, gastrointestinal tract (Yu et al., 2016), skeletal muscle, kidney, adipose tissue, heart, vasculature, and nervous system (Zhu et al., 2011). Although TRP channels and their ligands are potential targets to treat obesity and diabetes in the field of metabolic diseases (Nilius and Szallasi, 2014), their roles in many metabolic processes are still controversial and being studied. Here we discuss the role of TRP channels in metabolism and suggest numerous avenues for future study.

TRP CHANNELS IN METABOLISM

Members of the TRP channels play important physiological roles and can be observed in cells in different metabolic states. They work as gatekeepers for the trans-cellular transport of several cations, including Ca^{2+} and Mg^{2+}, but their biological roles are diverse (Table 1) (Nilius and Owsianik, 2011).

TRPA

TRPA1 is a receptor for a broad range of environmental oxidants and irritants and has a central role in pain and other preclinical conditions (Julius, 2013). It is directly activated by cinnamaldehyde, allyl isothiocyanate (AITC), allicin, formalin, and icilin (Bessac and Jordt, 2008; Macpherson et al., 2007; Trevisani et al., 2007). In association with cinnamaldehyde, TRPA1 drives insulin and ghrelin secretion, enhances insulin sensitivity in the CNS and reduces the deposition of fat in the liver. Supplementing AITC with a high-fat diet causes less weight gain compared with high-fat diet alone in mouse model (Ahn et al., 2014). *Drosophila* TRPA1 (dTRPA1) is highly expressed in the posterior dorsal ganglion of the fly brain and the axon bundles of the place are sent to the sub-esophageal zone, which is a primary center to regulate feeding (Lee, 2013). This indicates possible direct control in metabolism of dTRPA1 in brain. Non-targeted metabolomic profiling revealed that mutations in dTRPA1 had a direct effect on the free fatty-acid metabolism and methionine salvage pathway. Furthermore, trehalose is a sugar associated with cellular processes for heat protection. This process is slightly upregulated in a *trpA1* mutant background (Lee et al., 2016). TRPA1 has a role in enteroendocrine L-cells of the intestine. The gut hormone, glucagon-like peptide 1 (GLP-1) has a crucial role in glucose metabolism. It acts via changing insulin secretion on the gut–brain axis. Administration of TRPA1 into the duodenum resulted in GLP-1 secretion from these cells. So higher levels of GLP-1 can be an alternative hallmark in antidiabetic therapy (Smeets and Westerterp-Plantenga, 2009). TRPA1 is also expressed in enterochromaffin cells that contain cholecystokinin (CCK). The activation of TRPA1 causes satiety in mice via CCK secretion (Nozawa et al., 2009). Methyl syringate, one of the TRPA1 agonists, decreases food ingestion and gastric emptying in mouse models (Kim et al., 2013). However, TRPA1 is also expressed in the tongue of mammals and insects (Kim et al., 2010; Xiao et al., 2008). It is possible that TRPA1 agonists can directly activate taste receptor cells to reduce ingestion. So it is combinatory effect in pheripheral as well as internal sensors.

TRPV

The TRPV channel subfamily has six members categorized into two groups: TRPV1-V4 and TRPV5-V6. TRPV1-V4 consists of the thermo-TRPs that are triggered by specific temperature threshold. Although TRPVs that are thermosensitive seem to function in sensing temperature changes, these channels are also present in tissues where dramatic temperature swings are prevented by thermoregulatory homeostasis. Thus, temperature may perform a permissive rather than essential role in controlling the activity of these TRPs (Lyall et al., 2004; Moqrich et al., 2005). TRPV5 and TRPV6 have a role to reabsorb Ca^{2+} from the kidney and intestine, respectively (Nijenhuis et al., 2005).

TRPV1 has a role in potential sensory nerves that innervate into pancreatic islets and adipose tissues for insulin production. These channels are expressed in several neuronal (from olfactory, basal ganglion to cerebellum) and non-neuronal (buccal cavity, intestine, stomach, liver, and pancreas) cells (Nilius and Szallasi, 2014; Seabrook et al., 2002). TRPV1 channel is activated by temperature threshold around 42°C, and hot pepper ingredient, capsaicin. Ingestion of capsaicin, the well-known TRPV1 agonist, prevents diet-induced obesity in mouse models (Kang et al., 2010). Adipose tissue expresses TRPV1, but the tissue isolated from obese animals including humans displayed reduced expression level of TRPV1 (Chu et al., 2003; Zhang et al., 2012). TRPV1 knock-out (KO) mice developed age-associated obesity and hypo-metabolism (Wang and Siemens, 2015). However, recent findings have indicated that the prevention of obesity as beneficial effects

Table 1. Receptors, activators and inhibitors of metabolic TRP channels

Subfamily	Locus	Activators	Inhibitors	Functions	References
TRPV					
TRPV1	Sensory neurons, brain, spinal cord, keratinocytes, pancreas, tongue, and bladder	Cannabigerol, capsaicin, gingerol, lysophosphatidic acid, piperine, N-oleoyldopamine, palmitoylethanol-amide, and vanillotoxin	Capsazepine, iodo-resinifera toxin, resolvin D2 thapsigargin, yohimbine, and BCTC	Taste, salivary secretion, thermoregulation, intestinal ion and fluid secretion, gastric hormone release, and insulin release	(Chu et al., 2003; Parks et al., 2010; Seabrook et al., 2002)
TRPV2	Brain, spinal cord, sensory neurons, spleen, and GI-tract	Camphor, incensole acetate, and lysophosphatidylcholine	Tranilast	Thermoregulation, insulin release, and glucose homeostasis	(Qin et al., 2008)
TRPV3	Brain, sensory neurons, and tongue	Farnesyl pyrophosphate and menthol	Isopentenyl pyrophosphate and resolvin D1	Taste, thermoregulation, and GI cancer	(Bang et al., 2010; 2011; Moqrich et al., 2005)
TRPV4	Brain, sensory neurons, kidney, heart, liver, spleen, and inner ear	Citric acid, dimethylallyl pyrophosphate, apigenin, and 4α-phorbol 12, 13-de decanoate	Resolvin D1, HC-067047, and RN-1734	Thermoregulation and pain	(Bang et al., 2012; Suzuki et al., 2003)
TRPM					
TRPM2	Brain, pancreas liver, and heart	ADP-ribose and cyclic ADP-ribose	Clotrimazole, N-(p-amylcinnamoyl) anthranilic acid, and econazole	Insulin secretion, diabetes, obesity, and CNS disorder	(Kraft et al., 2006; Perraud et al., 2005)
TRPM4	Pancreas, colon, bladder, and heart	BTP2	9-phenanthrol and flufenamic acid	Insulin release and bladder function	(Grand et al., 2008; Takezawa et al., 2006)
TRPM5	Brain, taste coil, pancreas, GI-tract, liver, and tongue	Rutamarin and steviol glycosides	NSAID drugs, nicotine, tri-phenyl phosphine oxide, and 2-APB	Taste, gastric hormone secretion, and insulin release	(Palmer et al., 2010)
TRPM8	Sensory neurons, liver, stomach, prostate, and bladder	Menthol, linalool, geraniol, hydroxycitronellal, WS-3, and frescolat MGA	AMTB, BCTC, benzimidazoles, and 5-benzyloxytryptamine	Taste and thermoregulation	(Parks et al., 2010; Peier et al., 2002)
TRPA					
TRPA1	PNS, hair cells, and enter-endocrine cells	15-deoxy-Δ12, 14-PGJ2, 4-hydroxynonenal, 4-oxononenal, and methylglyoxal	Camphor, menthol, resolvin D1, and resolvin D2	Taste, thermoregulation, and gastric hormone release	(Macpherson et al., 2007; Xu et al., 2005)
TRPML2	CNS, pancreas, and intracellular ion channels	SF-51, ML-SA1, SID24801657, and SID24787221	Adenosine deaminase (ADA)	Mucolipidosis	(Shen et al., 2012)

Subfamilies of TRPA, TRPV, and TRPM are principal cationic channels having roles in body metabolism. TRP channels are regulated by various exogenous and endogenous activators and inhibitors. Their receptors and functions in metabolic aspects are listed.
BCTC, N-(4-Tertiarybutylphenyl)-4-(3-cholorphyridin-2-yl)tetrahydropyrazine-1(2H)-carbox-amide; GI, gastrointestinal; ADP, adenosine diphosphate; NSAID, nonsteroidal anti-inflammatory drug; AMTB, N-(3-Aminopropyl)-2-[(3-methylphenyl)methoxy]-N-(2-thienylmethyl) benzamide hydrochloride; MGA, menthone glycerin acetal; PNS, peripheral nervous system.

seem to be minute and would in all probability require daily long-term intake of capsaicin (Saito and Yoneshiro, 2013; Whiting et al., 2014). While consuming a standard chow diet, TRPV1 KO mice showed normal insulin sensitivity, with comparable glucose metabolism rates to wild-type mice (Lee et al., 2015). Interestingly, TRPV1 KO mice were also protected from obesity caused by diet and exhibited an increased longevity, which correlated with the prolongation of a juvenile metabolic profile (Motter and Ahern, 2008).

In addition, TRPV1 is found to participate in multifaceted

metabolic functions in various other tissues, including the adipose tissue, hypothalamus, and the gastrointestinal tract (Baboota et al., 2014). However, the exact roles underlying their protective functions in these tissues remain obscure. Relying on the metabolic state and cell type, TRPV1 has been a positive inducing factor for metabolic homeostasis. Activation of TRPV3 triggers inhibition of the phosphorylation of insulin receptor substrate-1 (IRS-1) and suppression of PPAR-γ, thus preventing lipid accumulation and adipogenesis (Bang et al., 2010; 2011; Ye et al., 2012). In brown adipose tissue (BAT), activation of TRPV4 negatively operates oxidative metabolism (Ye et al., 2012). The loss of TRPV4 results in a rise of oxidative potential in skeletal muscle by a compensatory regulatory mechanism (Kusudo et al., 2011). Interestingly, creating TRPV4 KO mice or antagonizing TRPV4 by pharmacologic blockade with glibenclamide elevates thermogenesis in adipose tissue and protects against adipose inflammation, diet-mediated obesity, and insulin resistance. TRPV4 in adipose tissue boosts pro-inflammatory cytokines (Bang et al., 2012; Ye et al., 2012).

TRPM

The TRPM subfamily is composed of eight members, which are categorized into three groups based on their structural homology: TRPM1/3, TRPM4/5, and TRPM6/7. TRPM2 and TRPM8 have relatively low sequence homology with the others and therefore they are not included in the group. TRPM2, TRPM6, and TRPM7 are distinctive among other TRPM channels because they have active enzyme domains in their C-termini merged to their transmembrane domains (Moran et al., 2011; Walder et al., 2009). TRPM2, TRPM3, TRPM4, and TRPM5 have been distinguished to contribute in the regulation of metabolism (Zhu et al., 2011).

TRPM2, TRPM3, TRPM4, and TRPM5 are present in rodent insulinoma cells and mouse islets. TRPM2, TRPM4, and TRPM5 have a role in the regulation of insulin secretion. TRPM2 and TRPM4 channels are present in insulin-producing pancreatic β-cells, and expression of dominant negative forms of TRPM4 and TRPM2 small interfering RNAs (siRNAs) decreases insulin secretion from the β-cells (Cheng et al., 2007; Grand et al., 2008; Kraft et al., 2006; Togashi et al., 2006). TRPM5 is also important for Ca^{2+}-activated cation channels in β-cells and GLP-1 secreting L-cells. Much like the TRPV1, the TRPM8 channel has a role in adipocytes (Fernandes et al., 2012; Parks et al., 2010; Rossato et al., 2014). Menthol is a known TRPM8 agonist which induces hyperactivity and suppresses diet-induced weight gain (Jiang et al., 2017; Peier et al., 2002). Menthol amplifies uncoupling protein 1 (UCP-1) expression in BAT in a dose-dependent way. However, this effect disappears in TRPM8 KO mice. Mice can be prevented from diet-induced obesity through prolonged dietary menthol supplements. In humans, TRPM8 activation can induce the browning of white adipose tissue (WAT browning), possibly by accelerating energy consumption (Rossato et al., 2014).

TRPM2 KO mice have deficits in insulin production under both high-fat or normal diet (Uchida and Tominaga, 2011). TRPM2 is broadly expressed in organs including the heart, brain, kidney and the immune system. It also functions as an oxidative stress sensor (Jang et al., 2014; Perraud et al., 2005). Moreover, TRPM2, TRPM4, and TRPM5 are controlled via CNS and have roles in neuronal activation, neurodegeneration, and cell death (Ramsey et al., 2006).

FUNCTIONAL CHARACTERISTICS OF TRP CHANNELS

Lipid metabolism

TRP channels have been shown to be key regulatory proteins involved in the process of lipid metabolism and energy homeostasis (Zhu et al., 2011). TRPV1 activation by capsaicin induces decreased triglyceride amounts in 3T3-L1 pre-adipocytes during adipogenesis. Similarly, capsaicin reduces dietary high-fat-induced hypertriglyceridemia in rats by exhibiting higher lipoprotein lipase movement in adipose tissues (Tani et al., 2004). Depending on the membrane lipid content, the localization, and function of TRP channel can be controlled. When methyl-β-cyclodextrin was treated in rat arteries as the cholesterol acceptor, membrane cholesterol is reduced, and *trpC1* expression level is decreased (Bergdahl et al., 2003). Similarly, cholesterol depletion in adult rat DRGs reduces TRPV1 levels in membrane, which induces decrease of TRPV1 currents mediated by proton or capsaicin (Liu et al., 2006). Furthermore, lysophosphatidylcholine (LPC) derived from phosphatidylcholine in cell membrane activates TRPC6 in cultured human corporal smooth muscle cells. LPC is one of major phospholipids of oxidized low density lipoprotein (LDL), which is an active pro-inflammatory lipid in pathological conditions (Rabini et al., 1994). Moreover, LPC and lysophosphatidylinositol (LPI) are able to induce TRPV2 activation. This activation mediated by Gq/Go and phosphatidylinositol-3,4 kinase (PI3,4K) signaling, seems to be mostly attributable to TRPV2 localization to the plasma membrane. It is highly dependent on the lysophospholipid head group and the length of the side-chain. In prostate cancer, metastasis of the cells is increased by TRPV2 activation by LPC and LPI (Monet et al., 2009). This may suggest a pathological role of TRPV2. Furthermore, 7-ketocholesterol, as a component of oxidized LDL, induces TRPC1 translocation to lipid rafts, activation of the channel, and increased calcium influx (Berthier, 2004).

Some studies have highlighted differences in intracellular Ca^{2+} concentration among normal and insulin-resistant cardiomyocytes by the application of bipolar lipids. Exogenous polyunsaturated fatty acids (PUFAs) bypass endogenous synthesis of PUFAs by eliciting TRPV1-dependent Ca^{2+} inward currents in sensory neurons (Kahn-Kirby et al., 2004; Lanner et al., 2008). Both cholesterol and sphingolipids as raft-enriched lipids may have effects on TRP channel activity, either via direct protein-lipid interactions or by affecting the physical properties of the lipid bilayer (Dart, 2010). Lipid signaling and lipotoxicity are strongly connected with oxidative metabolism. As a result, lipid agonists or modulators of TRPC channels are subject to oxidative modification (Svobodova and Groschner, 2016).

Glucose metabolism

Hyperglycaemia significantly increases TRPC6 in platelets, whereas expression of other TRPC members remain the same (Liu et al., 2009). GLUT4 is a glucose transporter protein,

which is highly expressed in mammalian adipose tissues and skeletal muscles (Huang and Czech, 2007). Unlike other cohorts of glucose transporters, GLUT4 responds efficiently to insulin. A variety of genetically engineered mouse models have been used to demonstrate the role of GLUT4 in maintaining whole body metabolism, including glucose homeostasis in muscles and energy sensors in adipocytes. However, GLUT4 KO mice show normal fat mass and adipocyte size, and normal glucose uptake in adipose tissues. GLUT4 is an energy sensor rather than a main regulator of glucose homeostasis in adipocytes (Yoshioka et al., 1995). Interestingly, TRPV1 KO mice showed longer life spans, with juvenile metabolic phenotypes, when their diet was supplemented with capsaicin, suggesting TRPV1 may cause diet-induced obesity in mice (Riera et al., 2014). In contrast, TRPM8 activation via diet supplements in mice was protective against diet-induced obesity (Rossato et al., 2014).

METABOLIC SYNDROME

TRP channels are widely present in the tissues including adipocytes, endothelial cells and vascular smooth muscles. So the deficits of TRP channels are highly related to numerous diseases and specifically related with the progression of varied cardiovascular diseases (Nilius et al., 2007). This explains their widespread functions. However, because they are widely distributed, disturbance in or alterations in expression of TRP channels may induce the development of metabolic syndrome (Table 2). Multiple channels such as TRPV1, TRPC3, TRPC6, and TRPC7 are activated essentially by diacylglycerol, whereas other TRPCs such as TRPC4, TRPC5, and TRPC6 are mainly activated after exhaustion of intracellular sarcoendoplasmic stores (Nilius et al., 2007). TRP channels may be directly affected by the agonists that were involved in the pathology of metabolic syndrome. For instance, angiotensin receptors are activated by angiotensin II. Series of ligand dependent activation cascade finally lead to the production of inositol triphosphate and diacylglycerol from phosphoinositide. These are the keys to open TRP channels, as elevation of diacylglycerol and depletion of inositol trisphosphate stores activate TRP channels (Bottari et al., 1993). The hetero-multimeric composition and expression of TRP channels maintain balance in the intracellular calcium homeostasis via transmembrane calcium influx. These functional alterations may develop metabolic syndromes (Liu et al., 2008).

Obesity

Obesity is the abnormal increase in body weight, as a sign of many of metabolic syndromes (Grundy, 2004). The TRPV1 channel is a key regulator of pre-adipocytes, appetite regulation, fat distribution, and obesity-induced chronic inflammatory responses. Both endogenous agonists (N-arachidonoyl dopamine and anandamide) and exogenous agonists (capsaicin and resiniferatoxin) may influence TRPV1 channel activity (Kumar et al., 2013). Application of capsaicin prevents adipogenesis and obesity in both mice and humans. Capsaicin increases intracellular calcium in pre-adipocytes but not in mature adipocytes, which is highly dependent on TRPV1 expression between pre-adipocytes and mature adipocytes (Xu et al., 2005; Zhang et al., 2007). However, when mice were fed on a high-fat diet, weight gain did not differ between TRPV1 KO and wild-type mice (Marshall et al., 2012). Moreover, ingestion of capsaicin with a high-fat diet did not block obesity in TRPV1 KO mice, although it affected obesity in wild-type (Zhang et al., 2007). This finding may be explained by another study that showed the phenotype of TRPV1 KO mice is dependent on age and environmental variables that have direct impact on thermoregulation (Wanner et al., 2011).

TRPV1 is expressed in visceral adipose tissues expressed in visceral as well as pre-adipocytes. When mice is fed with high sugar (high diet food) supplemented with TRPV1 agonist mono-acyl glycerol, it prevents white fat accumulation, activating mitochondrial UPC1 in BAT. Comparing obese male mice with their lean counterparts, the level of TRPV1 is alleviated in visceral tissues. Moreover, ingestion of capsaicin with a high fat diet did not block obesity in TRPV1 KO mice, although it affected obesity in wild type (Zhang et al., 2007). This activation of TRPV1 leads to PPAR-γ activation, nuclear factor NF-kB inactivation, the secretion of pro-inflammatory mediators by macrophage activation, and inhibition of obesity-associated macrophage migration. The obesity induced chronic inflammatory responses have major role in the developmental process of atherosclerosis and type II diabetes mellitus (T2DM) (Masuda et al., 2003). Endogenous TRPV1 agonist, N-oleoylethanolamide activates vagal sensory afferent neurons that regulate calorie intake and appetite. This phenomenon is investigated only in wild type mice, because only wild type mice showed decreased food consumption, suggesting that TRPV1 activation may control appetite (Wang et al., 2005).

Some TRPV members (V1-V4) have been proven to play pivotal roles in adipocytes. TRPV3 is highly expressed in adipocytes, and its activation prevents lipid buildup and adipogenesis (Cheung et al., 2015; Qin et al., 2008). In contrast, only TRPV1, TRPV2, and TRPV4 may have roles in 3T3-F442A pre-adipocytes. TRPV4 is highly expressed in this cell line, which confirms previous observation that exhibit TRPV4 expression in adipose tissue (Liedtke et al., 2000). Subcutaneous adipose tissue of TRPV4 KO mice showed higher UCP1 levels compared with control mice. Taken together, TRPVs results in having significant functions in adipocytes (Suzuki et al., 2003; Zsombok and Derbenev, 2016).

TRPM5 is a common downstream ion channel in type 2 taste receptor cells for GPCRs, which sense the basic tastes of sweet, umami, and bitter (Sprous and Palmer, 2010). Genetic changes in TRPM5 completely impaired the ability of mice to detect not only various tastes but also fat (Liu et al., 2011). Blocking TRPM5 in taste cells reduces appetite, so it can be a strategy to lose weight (Palmer and Lunn, 2013; Palmer et al., 2010; Sprous and Palmer, 2010). Quinine as a TRPM5 blocker induces weight loss in a mouse model (Cettour-Rose et al., 2013). Similarly, but inversely, levels of the fat hormone, adiponectin, are correlated with the amount of fat. Thus, overexpression of adiponectin increases energy expenditure and as a result, induces a lean body type. Blocking TRPC5 channels results in increase of plasma adiponectin, which can be beneficial to patients with metabolic disorders such as obesity and T2DM (Palmer and Lunn, 2013).

Table 2. Involvement of TRP channels in each metabolic syndrome

Subfamily	Receptor	Functions in obesity	Functions in diabetes	Functions in mucolipidosis	References
TRPV	TRPV1	Reduction in adipogenesis, appetite control, fat distribution, obesity-induced chronic inflammatory responses, and TRPV1 activation increase liver function	Islets inflammation and insulin resistance, progression to T1DM	-	(Zhang et al., 2007)
	TRPV2	TRPV2 activation negatively regulate BAT differentiation, reduce lipid accumulation, KO mice has more WAT with HFD induced obesity	TRPV2 inhibition cause glucose induced insulin secretion	-	(Suzuki et al., 2003; Uchida et al., 2017)
	TRPV3	Activation prevent lipid build-up and adipogenesis	-	-	(Cheung et al., 2015)
	TRPV4	Regulate UPC1 level in subcutaneous adipose tissue, negatively regulate oxidative metabolism, TRPV4 KO protect from adipose inflammation, diet-mediated obesity, and insulin resistance	-	-	(Ye et al., 2012)
TRPML	TRPML1 & TRPML2	-	-	*trpml* mutation causes pupal lethality, autophagy for nutrition, amino acid deprivation. Impairment in vascular carbohydrate, lipid and protein metabolism	(Venkatachalam et al., 2013)
TRPM	TRPM2	TRPM2 KO are resistant to diet induced obesity and inflammation	Increase calcium level, induce insulin secretion from pancreatic islets, KO reduce inflammation in adipose tissue and liver	-	(Zhang et al., 2012)
	TRPM3	-	Regulate zinc level, trigger insulin secretion from beta-cells	-	(Colsoul et al., 2013)
	TRPM4	-	Glucagon synthesis from alpha cells, indirect role in insulin synthesis	-	(Colsoul et al., 2013)
	TRPM5	Basic taste regulator, control appetite and obesity	Increase insulin secretion and glucose tolerance, regulate plasma insulin level	-	(Palmer et al., 2010)
	TRPM6	-	Balance serum magnesium level, reduce possibility of T2DM	-	(Walder et al., 2009)
	TRPM8	TRPM8 activation induces browning of WAT, induces UPC1 expression in BAT	-	-	(Rossato et al., 2014)
TRPA	TRPA1	Activation cause satiety and control obesity	Activation induce insulin secretion from beta cells	-	(Macpherson et al., 2007)

This table provides specific TRP channels associated with obesity, diabetes, and mucolipidosis.
T1DM, type 1 diabetes mellitus; HFD, high fat diet.

Diabetes

It is experimentally proven that several TRP channels have a practical role in the onset of diabetes mellitus (Liu et al., 2008). Among different TRPVs, TRPV1 has been found to control islets inflammation and insulin resistance by activating its associated pancreatic sensory neurons. Ablating TRPV1-associated pancreatic sensory neurons in diabetes-prone mice prevents developing diabetes and insulitis. This indicates

that pathogenesis of type I diabetes mellitus is associated with TRPV1 activation (Razavi et al., 2006). Insulin signaling promotes mitochondrial oxidative capacity and ATP production. TRPA1 is abundant in rat pancreatic β cells (Colsoul et al., 2013). TRPA1 agonists such as mustard oil and 4-hydroxy-2-nonenal induce insulin secretion in pancreatic β cells. Furthermore, the TRPA1 antagonist including HC-030031 hinders insulin release induced by glucose increase. This provides the evidence that TRPA1 has a direct role to control insulin secretion (Leibiger et al., 2002).

TRPM2 activation induces calcium increase into pancreatic islets, and increases in the level of cyclic ADP-ribose. This results in regulating insulin secretion (Togashi et al., 2006). Reactive oxygen species (e.g., H_2O_2), glucose, and incretins are stimuli for the activation of TRPM2 (Uchida and Tominaga, 2011). TRPM2 KO mice are more sensitive to insulin because of increased glucose metabolism in their heart arising from the phosphorylation of elevated Akt and glycogen synthase kinase 3. TRPM2 KO mice also reduce inflammation in the adipose tissue and liver (Zhang et al., 2012). These evidences demonstrate that TRPM2 has a role in metabolism. Expression of TRPM2, TRPM4, and TRPM5 has been found in human islets of Langerhans, suggesting that they may regulate pancreatic function and insulin secretion (Colsoul et al., 2013; Takezawa et al., 2006).

Mucolipidosis

Lysosomal storage disorders are metabolic diseases characterized by a deficiency in the enzymes that are important for vesicular lipid, carbohydrate, and protein metabolism (Futerman and Van Meer, 2004). Four types of mucolipidosis have been identified based on their physiology and pathophysiology (David-Vizcarra et al., 2010). Mucolipidosis type IV (MLIV) is an autosomal recessive disorder, generated by mutations in transient receptor potential mucolipin 1 (TRPML1). In MLIV, TRPML1, a vesicular Ca^{2+} release channel, is non-functional. TRPML1 contributes to the fusion of amphisomes with lysosomes. Other types of mucolipidosis are caused by non-functional metabolic enzymes. These include mucolipidosis I (sialidosis), caused by aberrant sialidase, and mucolipidosis II and III, caused by mutated N-acetylglucosamine-1-phosphotransferase (Shen et al., 2012; Tiede et al., 2005; 2006). In *Drosophila*, a null mutation of *trpml* leads to pupal lethality, when the flies count to autophagy for nutrition. This pupal lethality is caused by reduced targets of rapamycin complex 1 (TORC1) signaling (Venkatachalam et al., 2013). This indicates that cellular amino acid starvation is one of the fundamental causes of toxicity in the TRPML deficiency. It raises the intriguing feasibility that neurological disorder in MLIV patients may therefore stem from amino acid deprivation. A high-protein diet can reduce pupal lethality and increase the amount of acidic vesicles. However, further inhibition of TORC1 activity by administering rapamycin worsens the *trpml* mutant phenotype. The severity of MLIV might be decreased with a high-protein diet (Wong et al., 2012).

CONCLUSION AND FUTURE PERSPECTIVES

TRP channels possess various metabolic functions which are thought to be key targets for different physiological processes. Glucose and lipid metabolism are the central pathways that maintain energy balance, thermal regulation, and control of the metabolome. Their dysfunction can cause metabolic diseases including obesity, diabetes, and mucolipidosis. The severity of these disorders can be diminished by the consumption of supplementary foods, such as capsaicin. However, the precise target of this supplementary dietary intake is not clearly understood because multiple tissues, such as adipose, pancreatic, and even CNS tissues may be modulated by these supplements. A systemic analysis would be required to reveal more of these mechanisms. Analysis of TRP channel mutated animals with regard to their metabolomes would help us to further understand TRP channel functions and related pathogenesis.

Disclosure

The authors have no potential conflicts of interest to disclose.

ACKNOWLEDGMENTS

S.D. was supported by the Global Scholarship Program for Foreign Graduate Students at Kookmin University in Korea. This work is supported by grants to Y.L. from the Basic Science Research Program of the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2016R1D-1A1B03931273 and NRF-2018R1A2B6004202).

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