TRPA1 in obesity and insulin resistance

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Abstract

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Short Running Title: - TRPA1 in metabolic complications

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Abstract

Transient receptor potential ankyrin 1 (TRPA1) channel is a calcium permeable, non-selective cation channel, expressed in the sensory neurons and non-neuronal cells of different tissues. Initially studied for its role in pain and inflammation, TRPA1 has now functionally involved in multiple other physiological functions. TRPA1 channel has been extensively studied for modulation by pungent compounds present in the spices and herbs. In the last decade, the role of TRPA1 agonism in body weight reduction, secretion of hunger and satiety hormones, insulin secretion and thermogenesis, has unveiled the potential of the TRPA1 channel to be used as a preventive target to tackle obesity and associated comorbidities including insulin resistance in type 2 diabetes. In this review, we summarized the recent findings of TRPA1 based dietary/non-dietary modulation for its role in obesity prevention and therapeutics.

Keywords: Transient receptor potential, Dietary modulators, Gut hormones, Insulin, Obesity

Introduction

Obesity has become a primary health concern during the 21st century. Due to its increasing prevalence since 1970 in several countries, obesity has been declared as a global pandemic(Blüher, 2019; Friedrich, 2017). It has been estimated that about 1.9 billion adults were overweight and 600 million were obese in 2013(Ng et al., 2014) and these numbers would increase significantly by 2030 affecting nearly 51% of the population worldwide (Finkelstein et al., 2012). Obesity is a multifactorial, chronic disease characterized by the excessive accumulation of fat which not only affects the quality of life but also leads to the development of many other metabolic complications(Manna & Jain, 2015). Obesity has been reported to be linked with insulin resistance, type II diabetes, cardiovascular diseases, dyslipidemia, kidney diseases and even cancer(Abdelaal, le Roux et al., 2017). The most pernicious outcome of the obesity is type 2 diabetes. Due to a strong correlation between obesity and the risk for developing type 2 diabetes, the twin epidemic of diabesity has become a global crisis. The global economic burden associated with the obesity is very high, with an estimated cost of US $2.0 trillion or 2.8% of the global gross domestic product (GDP)(Tremmel, Gerdtham et al., 2017). At the same time, diabetes has grown very rapidly in both developed and low-income developing countries. It has been reported that in 2019, 463 million people were diabetic worldwide, and if actions were not taken to prevent the disease, this number would reach 578 million by 2030 and 700 million by 2045(Saeedi et al., 2019). The health care burden associated with diabetes is too high, with an estimated global health expenditure of USD 760 billion in 2019 and is estimated to reach USD 825 billion by 2030 and USD 845 billion by 2045(Williams et al., 2020).

Imbalance in the energy intake and energy expenditure has been linked to the development of obesity, that further leads to the progression of insulin resistance. In this context, targeting gut hormones controlling total dietary intake, adaptive thermogenesis and enhancement of energy expenditure are of great importance to deal with the progress of the disease(Church & Martin, 2018; Rodgers, Tschöp et al., 2012). Lifestyle modifications including diet management and physical activity, are salient factors to manage and prevent diabesity. The most common treatments for diabesity are pharmacological interventions, including drugs targeting insulin secretion from the pancreas, or incretins which improves glucose homeostasis and administration of insulin(Pappachan, Fernandez et al., 2019). Despite available treatments and interventions, there is a continuous race for the development of new therapeutics for diabesity.

Transient receptor potential (TRP) channels superfamily is comprised of a large group of cation permeable channels(C. L. Huang, 2004). Till date, there are 30 known channels of this superfamily and based on their sequence homology, these channels have been divided into 7 families i.e., TRPV (*V* anilloid), TRPC (*C* anonical), TRPM (*M* elastatin), TRPA (*A* nkyrin), TRPP (*P* olycystin), TRPML (*M* ucolipin) and

TRPN (*N* OMP-C)(Nilius & Flockerzi, 2014; J. L. Wu, Sweet, & Clapham, 2010). TRP channels which are expressed in neuronal and non-neuronal tissues, have different physiological functions such as sensory (vision, hearing, taste perception, nociception olfaction, thermo-sensation, and mechano-sensation), cell survival, growth and homeostasis (absorption and reabsorption of ions and fluid flow)[See review(Nilius & Owsianik, 2011)]. Recent evidences from the *in-vitro* as well as*in-vivo* studies revealed the presence of these channels in different organs including adipocytes, hypothalamus, liver, pancreas and intestine and their potential role in maintaining energy homeostasis [See review (Bishnoi, Khare, & Brown, 2018)].

TRPA1 which owes its name due to the presence of long 14 ankyrin repeats at N-terminal, is a calcium permeable, non-selective cation channel activated by a wide variety of noxious chemical, mechanical and environmental stimuli, pungent compounds present in herbs and plants as well as by many environmental toxins(Zygmunt & Högesättt, 2014). The important cellular factors responsible for modulating the TRPA1 channel activity include intracellular calcium ion concentration(Zurborg, Yurgionas et al., 2007), pH(Fumitaka Fujita et al., 2008), reactive oxygen(Arenas et al., 2017), nitrogen and carbonyl species[for more details refer to review by (Talavera et al., 2020)]. TRPA1 is largely known for its role in pain, neurogenic inflammation, itch*etc* .,(Xiao & Patapoutian, 2011) but continuous growing evidence from many experiments suggested the importance of TRPA1 channel in other physiological functions including gastric motility, insulin secretion and in the prevention of weight gain(Kagawa, Ozaki-Masuzawa et al., 2019; Khare et al., 2016; M. J. Kim et al., 2013). The present review focuses on TRPA1 structure, its physiological importance, channel modulation by agonists and antagonists, its role and possible mechanisms in prevention and therapeutics of obesity and related complications.

1.1 TRPA1 gene and protein structure

Transient receptor potential ankyrin or TRPA1 is the only member of the TRPA subfamily(Clapham, Montell et al., 2003). It was first cloned in 1999 by Jacquemar *et al* ., from lung fibroblasts(Jaquemar, Schenker et al., 1999). TRPA1 gene comprises of 73635 bases, 29 exons and is present on chromosome 8^{th} in the humans. Homologous genes of TRPA1 has been identified in both mammalian species like dog, non-human primates, cattle, pigs and non-mammalian species including birds, fishes, nematodes etc.(Talavera et al., 2020). In mammals, there is only one homologue of the TRPA1 gene but non-mammalian species do have more than one homologue of the TRPA1, for example, Drosophila has 4 homologues of TRPA1 gene and Zebrafish has 2 homologues of the TRPA1 gene(Nilius, Appendino et al., 2012). The TRPA1 protein consists of about 1100 amino acids with slight variation from one species to another (human TRPA1-1119 amino acids, mouse-1115 amino acids and rat-1125 amino acids)(Nilius et al., 2012). The average molecular weight of TRPA1 protein is between 120kDa and 130kDa.

The TRPA1's structural topology is very similar to other TRP proteins. TRPA1 is a homo- or hetero tetrameric non-selective cation channel. Each subunit of TRPA1 consists of six transmembrane alpha helices (S1 to S6), pre-S1 helix, linker domains connecting cytosolic domains to the transmembrane domain, β-sheets, TRP like domain and intracellular NH2 and COOH terminal (figure 1) (Cvetkov, Huynh et al., 2011). Paulsen*et al* . in 2015 used single particle electron cryo-microscopy (˜4 Å resolution) to reveal a large part of structure of human TRPA1. A re-entrant pore loop is present between S5 and S6 helix with two restriction points or gates. The upper gate is restricted by two diagonally opposed Asp 915 to accommodate calcium ions, on the other hand, the lower gate consists of two hydrophobic seals formed by Ile957 and Val961, that constrain the entry of rehydrated cations(Paulsen et al. 2015). TRPA1 has a very long N-terminal array of ankyrin repeats, in fact, the longest ankyrin repeat domain (ARD) among the other invertebrate TRP channels, consisting of 14-18 ankyrin repeats (humans have 16 ARD whereas mouse has 14 ARD)(Gaudet, 2008; Story et al., 2003). Each ARD is 33 amino-acid long sequence, arranged as an anti-parallel helix turn helix structure. The N-terminal ankyrin repeats play a major role in the protein-protein interactions, provides elasticity to the channel structure and is involved in the membrane trafficking of the TRPA1. Indeed, ARD deletion accounts for low or no insertion of the TRPA1 in the plasma membrane(Nilius, Prenen et al., 2011). Chimeric studies have revealed that the AR domain can be divided into two parts i.e., a primary module composed of AR10 to AR15 and an enhancer module composed of

AR 3 to AR8, contributing to the channel modulation in the mammals and snakes respectively(Cordero-Morales, Gracheva et al.,2012). Recently, it has been identified that the N-terminus, the pre-S1 helix and linker domain harbor the key cysteine and lysine residues (C622,C642,C666, K710), required for the channel activation by electrophilic and non-electrophilic agonists(Bahia et al., 2016; Samanta, Kiselar et al., 2018). In some of the non-mammalian species like snakes and insects, TRPA1 is activated by heat and low response has been observed to electrophilic activators(Gracheva et al., 2010; Sokabe, Tsujiuchi et al., 2008). Notably, in TRPA1, there is a pre S1 helix that connects ARD to the S1 region and is an important site where electrophilic agonist reacts with the key cysteine and lysine residues during interactions(Macpherson et al., 2007; Paulsen, Armache et al., 2015b). The TRP like domain, present right after the S6 helix at the C-terminus makes contact with non-contiguous structures including the pre-S1 helix, linker region in the N-terminus and S5-S6 linker region to regulate the allosteric modulation of the channel(Paulsen et al. 2015).

1.2 TRPA1 expression pattern and membrane trafficking

Initially, it was believed that the TRPA1 channel expressed in the sensory neurons of dorsal root ganglia (DRG), trigeminal ganglia(TG) and nodose ganglia, is primarily involved in the nociception(Story et al. 2003; Bautista et al. 2005). However, growing evidences from different studies suggested non-neuronal expression of TRPA1 in various organs including the heart, lungs, brain, pancreas, gastrointestinal tract and urinary bladder *etc.* (De Logu et al., 2019; Kannler et al., 2018; Z. Wang et al., 2019). In the DRG, TRPA1 is highly expressed in small and medium-sized peptidergic afferent neurons (Nagata, Duggan et al., 2005; Patil et al., 2020), contrarily, there are reports which showed the expression of TRPA1 in non-peptidergic neurons (IB4 positive neurons) as well(Barabas, Kossyreva et al., 2012). TRPA1 expression on these sensory neurons is also associated with expression of neurotransmitters like CGRP and substance P, that are involved in nociception(Bautista et al., 2006; Peixoto-Neves, Soni et al., 2019). In the trigeminal ganglion (TG), unmyelinated and small myelinated neurons have TRPA1. TRPA1 expression is also detected in trigeminal sensory nuclei (TSN), the spinal dorsal horn (DH) and terminals of the superficial laminae of the trigeminal caudal nucleus (Vc)(Y. S. Kim et al., 2010; Zanotto, Merrill et al., 2007). In the spinal cord, substantia gelatinosa (SG) is a key site for receiving noxious inputs. Pre-synaptically located TRPA1 has been reported to transmit the noxious inputs by mediating glutamate release, hence, initiating a synaptic transmission onto the SG neurons(Inoue, Fujita et al., 2012). TRPA1 is also involved in the presynaptic glycinergic neurotransmission in the dorsal root horn(Cho, Jeong et al., 2012).

In the autonomic nervous system, TRPA1 expression has been reported in SCG (Sympathetic superior cervical ganglia) region(Smith, Beacham et al., 2004), although similar reports from other groups have failed to find the TRPA1 expression at RNA level in the SCG region(Nagata et al., 2005). TRPA1 has been associated with glutamate release in the brain stem(Sun, Bang et al., 2009; Yokoyama et al., 2011). Astrocytes, found throughout the brain, contribute to synapse formation and regulate neuronal functions. Since, TRPA1 is expressed in astrocytes, it has been speculated that TRPA1 can modulate neuronal functions too(Shigetomi, Jackson-Weaver et al., 2013). The presence of TRPA1 in the hippocampus has been reportedly linked with the activation of cannabinoid receptor(Koch et al., 2011). Enterochromaffin cells and myenteric nerves present in the small and large intestine also express TRPA1(Kong et al., 2016; Nozawa et al., 2009; T. et al., 2010). In the colon, pelvic neurons express TRPA1, axons of which originates from the DRG neurons at thoracolumbar and lumbosacral spinal levels(La, Schwartz et al., 2011). In the stomach, the pyloric region showed the expression of TRPA1 but not the cardia region as confirmed by quantitative Real-Time PCR and*in-situ* hybridization (Camacho et al., 2015). In the gastrointestinal tract, TRPA1 acts as a chemo-sensor for various stimuli from the luminal environment and modulates the function in the intestine along with intestinal odorant receptors(Kaji, Karaki et al., 2011). High TRPA1 expression has been detected in rat pancreatic beta islets(Cao et al., 2012). In addition to the neuronal expression of TRPA1 channel in various organs, non-neuronal expression of TRPA1 has been identified in lungs(Caceres et al., 2009; Nassini et al., 2012), mouse inner ear(Corey et al. 2004; Stepanyan et al. 2011), keratinocytes, fibroblasts(Jain et al.. 2011), enterochromaffin cells of human and rat colon (Doihara et al., 2009), melanocytes(Atoyan, Shander et al., 2009), and human dental pulp fibroblast(El Karim et al.. 2011)(**figure 2**).

The expression of TRPA1 on the cell membrane in different organs is modulated by several kinases and cellular regulators. Protein kinase A (PKA) and Phospholipase C (PLC) signaling play an important role in the maintenance of TRPA1 on the membrane(Bandell et al., 2004). Application of TRPA1 ligand mustard oil (AITC) and pharmacological activators of PKA/PLC signaling increased the expression of TRPA1 on the membrane by enhancing the SNARE (SNAP receptor) mediated vesicle fusion. Both stimuli have been reported to increase TRPA1 expression *in-vitro*in HEK293 cells. However, treatment with tetanus toxin attenuates the TRPA1 response to the second pulse of mustard oil in the cultured DRG neurons. Importantly, translocation or vesicular exocytosis of TRPA1 to the membrane depicts one of the mechanisms for increased expression of the protein during inflammation or when treated with agonists. Moreover, blockade of protein kinase A (PKA) and phospholipase C (PLC) signaling reduced mustard oil mediated increased expression of TRPA1 on the membrane(Schmidt et al. 2009). In an another experiment with non-electrophilic agonist carvacrol, TRPA1 expression was not found to be increased on the membrane, indicating the significance of the electrophilic nature of agonist in the trafficking of channel protein to the membrane(Meents, Fischer et al., 2016). Phosphorylation by Serine/Threonine kinases has been reported as an important modulator for subcellular targeting and gating of many TRP channels(Voolstra & Huber, 2014), but very little is known for this kind of modification in TRPA1 channel. The extensive large tandem ankyrin repeats present at the N-terminus of TRPA1 channel is a vital regulator of channel trafficking to the cell membrane, subcellular localization and homo-tetramerization of the channel protein. Cyclin dependent kinase 5 (Cdk5), is a member of the CDK (cyclin dependent kinase) family, primarily known for its role in mitosis(Cicero & Herrup, 2005), also regulates pain signaling pathways(Kumar Pareek, 2012; Utreras, Futatsugi et al., 2009). TRPA1 was found to be a substrate of Cdk5 phosphorylation, where Cdk5 modulates the channel activity or response to its agonists(Hall et al., 2018). Cdk5 has been investigated by Sulak *et al* ., for TRPA1 modulation in the DRG neurons and TRPA1 transfected HEK293 cells. They reported that serine 448 (S448) located in AR12 (Ankyrin repeat domain 12) domain of the TRPA1 channel acts as a target for direct phosphorylation by Cdk5 in the DRG sensory neurons. Cdk5 inhibition by roscovitine attenuated TRPA1 response to its agonists in DRG neurons but failed to abolish TRPA1 response to the agonists in transfected HEK 293 cells (Sulak, Ghosh et al., 2018). In a similar report, it has been reported that threonine 673 (T673), present outside the ankyrin (AR) domain in TRPA1, was the only possible site for phosphorylation by Cdk5(Hynkova, Marsakova et al., 2016). PKA, PLC, or Cdk5 mediated phosphorylation of the TRPA1 channel required a scaffolding A-kinase anchored protein (AKAP) which directly interacts with the TRPA1 to increase the basal phosphorylation of channel protein(Zimova et al., 2020).

Inflammation also induces trafficking of TRPA1 to the membrane. TNF-α increases the membrane expression of TRPA1. Inflammatory cytokines mediated trafficking is dependent on SNARE proteins including VAMP1 and Snap 25(Meng et al. 2016). Other than inflammatory signals and chemical agonists of the channel, temperature also modulates the TRPA1 expression. It has been found that both cold (below 4°C) and high (49°C) temperature stimulates TRPA1 expression(May et al. 2012).

The tumor suppressor gene CYLD affects the post-translational level of TRPA1 inside the cell. CYLD is a ubiquitin hydrolase enzyme that deubiquitinates the TRPA1 channel, hence increases the TRPA1 protein in the cell. However, oncogenic mutation of CYLD could affect the cellular expression of the TRPA1 protein(Stokes et al. 2006). Thus, ubiquitination pathways could be an important mechanism that regulates the cellular level of TRPA1. Another cellular regulator of TRPA1 is AMPK, the energy sensor of the cell. Activation of AMPK negatively regulates the expression of TRPA1 on the membrane. In DRG neurons, AMPK activity lowers after glucose treatment and simultaneously TRPA1 expression increases on the membrane(Wang et al.2018). Membrane components like cholesterol and lipid rafts also play an essential role in the maintenance and functionality of TRPA1 on the plasma membrane. Disruption of lipid rafts and depletion of cholesterol reduces the response of the channel towards AITC and its sensitivity to the chemical stimulation(Sághy et al., 2015). Recently, it has been found that TRPA1 localizes in the cholesterol rich domain in the plasma membrane as revealed by total internal fluorescence microscopy and density gradient centrifugation(Startek et al., 2019).Despite extensive reports on TRPA1 structure, its agonists-antagonists and physiological functions, molecular mechanisms underlying its intracellular regulation and maintenance

are largely unknown. TRPA1 expression is modulated by both temperature and inflammatory cytokines but whether both use the same pathways is not clear. Similarly, membrane trafficking using SNARE dependent vesicular exocytosis has been exploited as a possible mechanism but ubiquitination pathways are still largely unknown. Further studies are required to get a clearer vision on channel modulation and trafficking.

TRPA1 Modulators

TRPA1 is activated by a variety of compounds including environmental irritants, pungent compounds, endogenous reactive mediators and pharmaceuticals (Bessac & Jordt, 2008). TRPA1 is a very attractive drug target for the development of analgesics and anti-inflammatory drugs, therefore pharmacology of this gating channel is of great importance. However, drug discovery efforts have been hampered due to the prominent differences between human and rodent TRPA1 homologues. It has been reported that many compounds which show agonistic effects with human TRPA1, can act as an antagonist in case of rodent TRPA1(Bianchi et al., 2012). A variety of compounds activate TRPA1 channel which can be broadly classified into two categories: electrophilic activators and non-electrophilic activators.

The first class of activators reacts with the thiol group of cysteine and lysine residue of the channel. With the help of mutagenesis, Hinman*et al* ., identified the key cysteine residues involved in the electrophilic activation of the TRPA1 channel. These cysteine residues were C619, C639, and C663 (C621,C641 and C665 according to the human TRPA1 sequence in Uniprot ID: O75762) present between the last ankyrin repeat domain (ARD) and first transmembrane segment (S1) of the cytoplasmic N-terminal of the channel(Hinman, Chuang, Bautista, & Julius, 2006). In mice, cysteine's C415, C422 and C622 (C414, C421 and C621 according to the human TRPA1 sequence in Uniprot ID: O75762), were identified by mass spectrometry and mutagenesis(Macpherson et al., 2007). Notably, mass spectrometric and cryo-electron microscopic studies have revealed C621 as an extraordinarily reactive site for electrophilic sensing in the TRPA1 channel(Bahia et al., 2016; Suo et al., 2020). Cysteine residues form the disulfide bridge when came in close proximity, potentially forming a ligand binding pocket. Mass spectrometric analysis of TRPA1 showed that upon binding with electrophilic agonists, there are conformational changes in critical cysteines (C193, C415, C463,C622, C634, and C666), along with some other cysteines (C31, C45, C66, C89,C105, C214, C259, C274, C541, C609, and C1087), hence support the above information that disulfide bonds are formed during binding between electrophilic activators and TRPA1 (Samanta et al., 2018). It has been reported that mutation of C633 and C651 which forms disulfide bonds lead to conformational changes in TRPA1 structure, making it non-responsive to electrophilic activators although there was a response to non-electrophilic activators(Babes et al., 2016).

Besides this continuously growing list of electrophilic activators of the TRPA1 channel, the other class of TRPA1 agonists comprises non-electrophilic compounds which modulate the channel without any covalent modifications. This class of activators has a wide range of compounds including natural compounds found in herbs like thymol (Lee et al., 2008), carvacrol (Xu, Delling et al., 2006), different classes of anesthetics(Leffler, Lattrell et al., 2011; Matta et al., 2008), nonsteroidal anti-inflammatory drugs (NSAIDs)(Hu et al., 2010) and different compounds used in therapeutics and cosmetics like parabens or alkyl esters of p-hydroxybenzoate(F. Fujita, Moriyama et al., 2007). Interestingly, some of the non-electrophilic modulators have bimodal action on TRPA1 activation and the best example of this is menthol (Karashima et al., 2007). Menthol which is a known TRPM8 agonist also activates mouse TRPA1 at low concentrations but inhibits the channel at higher concentrations(Karashima et al., 2007). Moreover it has been shown that menthol activates the human TRPA1, whereas non-mammalian TRPA1 does not respond to menthol, showing species differences of the channel(Xiao et al., 2008). Caffeine found in coffee represents another compound that showed species differences in the activation of TRPA1. Caffeine acts on amino acid Thr231 and Asp287 at the distal N-terminal region in mouse TRPA1 only, not in human TRPA1(Nagatomo & Kubo, 2008).

The list of various electrophilic and non-electrophilic compounds has been listed in Table 1.

The great importance of TRPA1 in pain, inflammation and many other diseases has initiated an increasing demand for the development of TRPA1 specific antagonists. The first TRPA1 antagonist was based on xanthine structure, symbolize as HC-030031 (Hydra Company), which was synthesized back in 2007. Glenmark

company has also disclosed some antagonists based on phtalimide derivates and imidazo-uridine derivatives (for more detailed information on synthetic antagonists please see reviews by Talavera et al., 2019 and Nilius et al., 2012). These commercially available antagonists are non-electrophilic in nature and modulate TRPA1 channel activity by non-covalent modifications. Interestingly, there are electrophilic antagonists too, several oximes have been reported to have antagonistic activity towards TRPA1. Oxime AP-18 possesses both agonistic and antagonistic activity against the TRPA1 channel(DeFalco et al., 2010). Some natural compounds also have antagonistic properties for TRPA1. Eucalyptol (1,8-cineole) is an ether monoterpenoid present in eucalyptus oil that inhibits human TRPA1 currents stimulated by AITC, menthol and octanol(Takaishi et al., 2012). The menthol analogue 4-isopropylcyclohexanol inhibits hTRPA1(Takayama, Furue et al., 2017). Camphor (derived from *Cinnamomum campharol)* , cinnamaldehyde and nicotine, all have been shown to have both stimulating and inhibitory effects on TRPA1 depending upon the concentration(Alpizar et al., 2013; Lee et al., 2008; Talavera et al., 2009).

2.1 TRPA1 and Natural Activators

A vast number of pungent natural compounds activate TRPA1 channel. The most important activator of this class is AITC, responsible for fresh flavor of wasabi and pungency of mustard oil(Uchida, Miura et al., 2012). Other than AITC, wasabi also contains 6-(methyl sulfinyl)hexyl isothiocyanate (6-MSITC) and 6-(methylthio)hexyl isothiocyanate (6-MTITC), which act as an electrophilic activator of TRPA1(Uchida et al., 2012).

Another prominent agonist of TRPA1 is cinnamaldehyde, found in the oil of cinnamon (*Cinnamonum verum)* (Bandell et al., 2004). Cinnamaldehyde has been reported to causes a burning or tingling sensation and pain stimulation if taken orally, due to the activation of TRPA1(Alenmyr, Herrmann et al., 2011).

Garlic is known for centuries for its medicinal properties including anti-bacterial, anti-fungal, anti-cancer, anti-inflammatory effects etc.(Bayan, Koulivand et al., 2014; Hosseini & Hosseinzadeh, 2015). Allicin, an organo-sulfur pungent compound of garlic, is an electrophilic activator of TRPA1(Bautista et al. 2005). Allicin also acts as a precursor for its other derivatives like diallyl sulfide, diallyl disulfide and diallyl trisulfide during metabolism. Allicin and its derivatives also activates TRPV1 at lower potency as compared to TRPA1, but efficacy of TRPV1 activation is lower than that of capsaicin(Koizumi et al., 2009; Macpherson et al., 2005). Ajoene, an allicin derivative, does not activate the TRPA1 channel but enhances the activation by other electrophilic compounds including AITC and allicin. Diethyl disulfide, an allicin related compound, found in Durian fruit also activates TRPA1 channel to mediate the hyper thermic effects(Terada et al., 2014).

S-alkyl-S-alkenyl disulfides, a rare class of natural products found in the *Ferula assa-foetida L* . potently activates TRPA1 channel suggesting the role of TRPA1 in the potential beneficial health claims associated with the use of asafoetida as a spice(Shokoohinia et al., 2013).

Phenol compounds like carvacrol and propofol activates human TRPA1(Woll et al., 2017; Xu et al., 2006). The pungency of oregano has been attributed to the carvacrol mediated TRPA1 activation(Xu et al., 2006). It has been observed that intra-epidermal injections of TRPA1 agonist carvacrol to the humans cause dose dependent pain sensations which were reduced in the presence of TRPA1 antagonist A-967079(Schwarz, Namer et al., 2017). Thymol, a monoterpene phenol derivative of cymene is present in oil of the thyme plant, has bimodal action on the TRPA1 channel similar to the menthol. Activation of TRPA1 by thymol desensitize the channel for further exposure to AITC or thymol(Lee et al., 2008).Monoterpenoids such as p-cymene-3-carboxylic acid, 3-amino-p-cymene(Ortar et al., 2012) and limonene(Kaimoto et al., 2016) also activates the TRPA1 channel.

6-gingerol, a phenol derived compound, found in the essential oil of fresh ginger and cloves, activates TRPA1(YANG et al.. 2016). Eugenol, a phenylpropene present in cloves stimulates TRPA1(Chung et al., 2014). Oleocanthal is a natural phenolic compound, responsible for the pungency of extra virgin olive oil. It has been demonstrated that oleocanthal dependent stimulation of rodent trigeminal nervous system requires functional TRPA1(Peyrot Des Gachons et al., 2011). Piperine and its related compounds isopiperine, isochavicine, piperanine, piperolein A, piperolein B, and N-isobutyl-(2E,4E)-tetradeca-2,4-diamide are responsible

for the spiciness of black pepper, also activate TRPA1(Okumura et al., 2010).

Ligustilide, found in *Apium graveolens, Levisticum officinale, Angelica sinensis* , *Ligusticum chuanxiong* , and North American traditional Medicine from *Ligusticum portieri*), is a potent activator and moderate inhibitor of TRPA1 channel. Its bimodal action does not depend upon concentration, rather on its aromatization. For example, aromatization of ligustilide produces dehydroligustilide that has been reported to have inhibitory effects on TRPA1(Zhong et al., 2011).

Curcumin, a principle curcuminoid of turmeric, acutely activates and subsequently desensitize TRPA1 in HEK cells (human TRPA1 transfected cells) and mouse sensory neurons. Curcumin showed no effects on TRPV1 or TRPM8(Leamy, Shukla et al., 2011). TRPA1 is also activated by non-pungent compounds like capsiate, dihydrocapsiate and nordihydrocapsiate (all these capsinoids are found in sweet chili) to lower potency than TRPV1(Shintaku et al., 2012). Fatty acids of royal jelly activates TRPA1(Terada, Narukawa et al., 2011). Artepillin C contributes to the pungency of Brazilian green propolis, activates TRPA1 channel more potently than known activator AITC(Hata et al., 2012).

Plants, fungi and animals produce terpenes which act as protectors from predators and foragers. These terpenes have unsaturated aldehyde moieties that activates the TRPA1 channel. For example, sesquiterpene isovelleral, polygodial, miogadial and miogatrial activates TRPA1. α-, β-eudesmol and γ-eudesmol are non-electrophilic sesquiterpenes which also activates TRPA1 channel(Escalera, Von Hehn et al., 2008; Ohara et al., 2017; Terada et al., 2019). In a recent report by Terada *et al* . in 2019, human TRPA1 is found to be activated by terpenes. These terpenes were part of essential oil obtained from the byproduct of daidai juice processing. Out of the total 10 terpenes tested, they found that 5 of them (linalyl acetate, geranyl acetate, osthole, geranyl propionate, and neryl acetate) activate human TRPA1 but not TRPV1 or TRPM8. This study was done using transfected cell line which requires further validation(Terada et al.. 2019).

Recently, it has been demonstrated that three natural compounds cuminaldehyde (present in cumin), p-anisaldehyde (present in anise) and tiglic aldehyde (present in onion/garlic) from spice's origin activate hTRPA1 in heterologous expression system and sensory neurons of DRG(Legrand, Merlini, de Senarclens-Bezençon, & Michlig, 2020).

Calcium ions dependent modulation

TRPA1 channel activity is modulated by a large number of endogenous activators including reactive oxygen species produced during inflammation, calcium ions, prostaglandins etc. Ca^{2+}, one of the ubiquitous and most important regulators of the channel has been reported to have both potentiating (at low concentrations) and desensitizing (at high concentrations) effects. Initial studies on TRPA1 channel activity suggested the possible role of extracellular calcium in the amplification of TRPA1 response to mustard oil or Δ^9-tetrahydrocannabinol (THC) in transfected HEK cells(Jordt et al., 2004). These effects were mediated by calcium entry through TRPA1 channel. Furthermore, these results were supported by Nagata *et al* ., they also speculated that extracellular calcium modulate the channel activity by binding to a site close to or within the channel(Nagata et al., 2005). TRPA1 channel modulation by Ca^{2+} is still a matter of debate. Extracellular calcium can also inactivate the channel; however, it has been shown that potentiation and inactivation of the TRPA1 *via*Ca^{2+} are two independent processes mediated by subsequent elevation in intracellular calcium ion concentrations(Y. Y. Wang, Chang, et al., 2008). The molecular mechanisms underlying Ca^{2+} dependent TRPA1 activation or inactivation are poorly understood. Initial reports demonstrated that Ca^{2+} ions bind to putative N-terminal EF hand motif of TRPA1 to activate the channel(Doerner, Gisselmann et al., 2007; Zurborg et al., 2007), but later studies showed that mutation in this region of TRPA1 does not affect the calcium dependent modulation of TRPA1(Nilius et al., 2011; Y. Y. Wang et al., 2008). An alternative hypothesis suggests that Ca^{2+} ions modulate TRPA1 channel activity by binding to acidic residues at the C-terminal. Deletion of 20 amino acids at C-terminal was reportedly does not affect the potentiation of the channel by Ca^{2+} ions or thiol-reactive groups, but reduces the Ca^{2+} dependent inactivation of the channel, thus supporting the potentiation-inactivation uncoupling mechanism. Simulations studies identified two amino acids (Asp1080 and Asp1082), critically important for the binding of Ca^{2+} ions at the

C-terminal (Sura et al., 2012). Taken together, these studies indicate that the conserved acidic residues in the C-terminus of the TRPA1 channel significantly affect the channel modulation by Ca^{2+} ions. Some conserved residues between transmembrane domain 2 (TM2) and transmembrane domain 3 (TM3) have been identified with the help of structural analysis and electrophysiology. These residues were E788, Q791, Y799, N805 and E808, however E788 alone was found to be responsible for the major regulatory effects of calcium ions(Zhao, Lin King et al., 2020). Intriguingly, these calcium binding residues are highly conserved among TRP channels including TRPM2, TRPM4 and TRPM8(Autzen et al., 2018; Diver, Cheng et al., 2019; Y. Huang, Winkler et al., 2018; Z. Zhang, Tóth et al., 2018). Calmodulin (CaM), an intracellular calcium dependent protein has been recently reported to play an essential role in maintaining the TRPA1 channel activity in response to calcium ions concentrations. Notably, C-lobe of CaM directly interacts with the 17 amino acids long non-canonical calmodulin binding domain (CaMBD) present at the C-terminus of the TRPA1 channel. CaM acts as a calcium sensor and mutation in either Ca^{2+}binding sites in CaM or CaM binding sites on TRPA1 renders the activation or desensitizing effects of calcium ions on TRPA1(Hasan, Leeson-Payne et al., 2017).

Role of TRPA1 agonism in prevention of diet induced Obesity

Obesity is a complex disease, resulted from the accumulation of excess fat in the body. There are many contributors to the development of obesity including endocrine disruptors, less sleep, cessation from smoking, less physical activity, various environmental and genetic factors. One of the important factors for the development of obesity is the imbalance in the energy expenditure which leads to the accumulation of fat in the different parts of the body. TRPA1 is majorly known for its role in pain sensation but growing evidence suggests its involvement in metabolic functions too. In this section, we have discussed the involvement of TRPA1 in regulating energy expenditure and thereby could be used as a target to combat weight gain, obesity and related complications.

4.1 TRPA1 in the gastrointestinal tract: General functions including ion transport, gastric emptying

As discussed earlier, TRPA1 is highly expressed in the gastrointestinal tract, distributed from stomach to colon. TRPA1 is found to be present in the enterochromaffin cells (EC cells), enteroendocrine cells of the intestine but not in the smooth layers or submucosal layers of the intestine(Nozawa et al.. 2009). Endocrine cells of the gut including enterochromaffin cells secrete neurotransmitters and hormones that regulate various gastrointestinal functions. One of the neurotransmitters that has been found to regulate the gastric motility and contractions is serotonin or 5-HT. It is also stored in enterochromaffin cells throughout the gut and is involved in the excitation of both intrinsic and extrinsic neurons, resulted in the modulation of many gastrointestinal functions (Gershon & Tack, 2007). TRPA1 agonist acrolein, AITC and cinnamaldehyde has been reported to stimulate the release of 5-HT from freshly isolated EC cells and RIN14B cell line(Nozawa et al., 2009). Similar studies with other TRPA1 agonists like methyl salicylate, eugenol, hypotonic solution and cold temperature stimulated the release of 5-HT from the EC cell, implicating its potential role in the regulation of gastric motility. These*in-vitro* studies were further supported by *in-vivo* effect of TRPA1 agonists like AITC, eugenol, thymol on gastric delaying through activation of the serotonergic pathway to stimulate the release of 5-HT from intestinal EC cells and mast cells(Doihara et al. 2009). These studies cumulatively showed that TRPA1 can act as luminal sensor in the intestine and could be used as a therapeutic target to regulate gastric motility.

TRPA1 expression in enterocytes of the duodenum and colon of mice also facilitates mucosal ion transport. TRPA1 agonists like AITC, cinnamaldehyde and linalool when applied to the luminal surface of duodenum and colon of the mice, stimulated short circuit ion current in the membrane. These experiments suggested the role of TRPA1 activation in the transepithelial ion transport, which has been linked to the fluid movement across the epithelium in the intestine. Also, there was no response in the presence of TRPA1 antagonists as well as in the TRPA1 knockout mice. Therefore, the presence of TRPA1 within the enterocytes is of great importance in terms of the absorption of nutrients from the intestine(Fothergill et al. 2016).

4.2 TRPA1 in BAT thermogenesis and modulation

Adaptive thermogenesis, refers to as the generation of heat in the body in response to external environmental stimuli has emerged as a potential option to counteract obesity. Brown adipose tissue (BAT) plays an essential role in the prevention of obesity due to a prominent role in the adaptive thermogenesis(Loh, Kingwell et al., 2017). BAT is characterized by the presence of uncoupling protein 1 (UCP1) and high mitochondrial content. UCP1, expressed in the inner membrane of BAT mitochondria, functions by uncoupling oxidative phosphorylation to generate heat and induction of thermogenesis(Fernández-Verdejo, Marlatt et al., 2019). Therefore, targeting BAT thermogenesis presents a suitable approach to enhance energy expenditure.

Adrenaline secretion from the adrenal gland has been linked to energy metabolism. It has been reported that capsaicin, a TRPV1 agonist induces adrenaline secretion in rats and increases the energy expenditure(T. Watanabe, Sakurada et al., 2001). Co-expression of TRPA1 with TRPV1 on the sensory neurons opens up the possibility of involvement of TRPA1 in elevating energy expenditure *via* adrenaline secretion. Iwasaki*et al.* in 2008 found that intravenous administration of AITC and cinnamaldehyde induce adrenaline secretion from the adrenaline gland in the anesthetized rats. They also showed that pre-treatment with the capsaicin diminishes the response in rats as capsaicin impairs the nerve functions(Iwasaki et al.. 2008). More energy consumption and thermogenesis due to adrenaline secretion could be due to the activation of the adrenergic receptor in BAT and upregulation of UCP1 protein in BAT tissue.

Similarly, a phenolic compound found in extra virgin olive oil; oleuropein aglycone reduces the total body weight, circulating plasma leptin and increases whole body thermogenesis by increasing the expression of UCP1(uncoupling protein) in BAT. Oleuropein activates both hTRPA1 and hTRPV1 expressed in HEK293 cells, with almost 10 times stronger potency for hTRPA1 over TRPV1. Consumption of oleuropein in high fat diet (HFD) fed rats reduces visceral fat through the activation of TRPA1 and TRPV1 followed by noradrenaline secretion *via* the β-2 and β-3 adrenoreceptors(Oi-Kano et al.. 2017).

Cinnamaldehyde is a pungent compound found in cinnamon, known to have many beneficial effects on metabolism, to check whether cinnamaldehyde intake could reduce fat accumulation, a study was conducted by Tamura*et al* . in 2012 on high fat and high sucrose (HFS) diet fed mice. Visceral fat accumulation (WAT accumulation) was found to be lower in HFS fed mice when cinnamaldehyde was added to the HFS diet(Tamura et al. 2012). A clinical trial conducted by Michlig *et al* . also provide evidence that a single dose of cinnamaldehyde (70mg/200ml; 300ppm) significantly increases the energy expenditure by a magnitude of 3.6 kcal over the period of experiment as compared to the placebo group(Michlig et al. 2016). Recent evidences also suggested the possible mechanism for the anti-obesity effects of cinnamaldehyde (Camacho et al., 2015; Neto, Boechat et al., 2020). Subcutaneous fat depots contain thermogenic adipocytes which play an important role in thermoregulation and metabolic health during cold exposure. Chronic treatment with cinnamaldehyde stimulated the thermogenesis in adipocytes *via*PKA/p38 MAPK dependent pathways(Jiang et al. 2017). In another report, it has been found that cinnamaldehyde administration to the HFD fed C57 mice leads to the browning of white adipose tissue. Upregulation of browning marker ucp1 along with higher expression of transcriptional factors like PPAR-γ (peroxisome proliferator-activated receptor gamma), PRDM16 (PRD1-BF-1-RIZ1 homologous domain containing protein-16) and PGC-1α (peroxisome proliferator-activated receptor gamma co-activator 1 α), leading to the browning of WAT has been reported along with anti-obesity effects of cinnamaldehyde(Zuo et al., 2017).

Royal jelly activates TRPA1 and TRPV1, stimulates energy expenditure and metabolism(Terada et al., 2011). In 2012, a human trial was conducted to evaluate the effect of royal jelly on body weight and dietary intake in diabetic patients. In the human trial, royal jelly supplementation resulted in a significant reduction in mean body weight (Pourmoradian et al.. 2012). In another set of experiment on HFD mice, royal jelly supplementation also reduced mean body weight, hepatic triglyceride content and stimulated BAT thermogenesis by increasing the expression of UCP1 protein in HFD fed mice. The possible mechanism for the body weight reduction is the activation of TRPA1 and thereby more thermogenesis and energy expenditure (Yoneshiro et al.. 2018).

Garlic is known for its beneficial properties for centuries. Garlic oil produced through steam distillation of raw garlic contains many sulfide compounds including diallyl disulfide (DADS), diallyl trisulfides (DATS), allyl sulfides, DAS (diallyl sulfides) and methyl allyl trisulfides (MATS). All these sulfide compounds which contribute to the goodness of garlic, are agonist of TRPA1 and TRPV1, where DATS (EC_{50} 0.49μmol/l) was reportedly found to be a more potent agonist of TRPA1 than AITC(EC_{50}1.47μmol/l)(Koizumi et al., 2009). Garlic oil consumption to the high fat diet fed rats reduces the overall weight and white adipose tissue (WAT) mass (significant reduction was found in epididymal and subcutaneous WAT) as compared to the control group. Surprisingly there was no difference in the energy intake but a variation in energy efficiency was observed. It was reported that garlic oil administration lead to more O2 consumption and fat oxidation in HFD fed rats. UCP1 protein, responsible for non-shivering thermogenesis was also upregulated in BAT after garlic oil consumption(Kagawa et al.. 2019). Allicin, a bioactive sulfide present in garlic also activate TRPA1 channel. Recently, it has been demonstrated that allicin administration to the HFD fed and Db/Db mice significantly increased BAT activity and energy expenditure. *In-vitro* experiments performed on isolated brown adipose tissues from mice showed that allicin directly activates BAT by upregulating the expression of UCP1 protein(C. Zhang et al., 2020). Cumulatively, these studies suggested the direct effect of TRPA1 agonists for the prevention of obesity by enhancing energy expenditure.

Stimulation of BAT activity provides an alternative to deal with the obesity. A clinical trial conducted by Matsushita *et al* ., showed that a single dose of Kaempferia extract increases the energy expenditure by the activation of BAT in healthy individuals. The probable mechanism for higher activity was supposed to be mediated through TRP channels like TRPV1 and TRPA1 as this extract contains various flavonoids but due to lack of vanilloid compounds in the extract, TRPA1 turn out to be the potential reason for this effect(Matsushita et al. 2015).

3T3-L1 cells are regularly used for studying adipogenesis related markers and targets. *trans* -pellitorine, an alkamide found in piper and macro-piper species has activation potential for both TRPV1 and TRPA1. Treatment of 3T3-L1 cells with trans-pellitorine reduced lipid accumulation. Furthermore, TRPA1 has been reported to play an essential role during early to intermediate stages of maturation of pre-adipocytes by reducing the expression of PPAR-γ and fatty acid synthase (FAS) enzyme in 3T3 cells when treated with trans pellitorine(Lieder et al. 2017). This data suggested the involvement of TRPA1 in lipid accumulation in adipocytes, however, *in-vivo*studies are required to confirm the same.

4.3 TRPA1 and secretion of Gut hormones

Energy expenditure is also regulated by gut hormones including ghrelin, cholecystokinin (CCK) glucagon-like peptide (GLP-1) and peptide YY (PYY). These hormones are either secreted in a state of hunger (ghrelin) or post-prandially (CCK, GLP-1 and PYY)(Murphy & Bloom, 2006). STC-1 cell line is a neuroendocrine cell line that provides a better*in-vitro* model to study the secretion pattern of both CCK and GLP-1 and to a lesser extent PYY(Purhonen, Louhivuori et al., 2008). STC-1 cells also express TRPA1 and treatment with AITC stimulated the secretion of satiety hormone CCK (Purhonen et al.. 2008). CCK is known for its role in regulating gastric motility, satiety, gastric emptying rate and appetite(Lean & Malkova, 2016). TRPA1 activation increases the intracellular calcium *via* calcium influx and it has been reported that calcium influx plays an important role in the secretion of CCK*in-vivo* . TRPA1 on the cell membrane when activated by agonists like AITC increases the influx of extracellular calcium into the cell which was blocked by the treatment with TRPA1 blockers. Their study demonstrated that calcium influx through activation of TRPA1 is required for the release of CCK from the STC-1 cell(Purhonen et al. 2008). Another group of scientists reported that di-unsaturated and mono unsaturated aldehydes activate TRPA1 to stimulate the secretion of CCK from STC-1 cells. There was reduced CCK secretion in the presence of TRPA1 antagonists and in the absence of extracellular calcium. Aldehydes were more potent than fatty acid and alcohol in terms of stimulation of CCK secretion in STC-1 cells(Nakajima et al.. 2014). Naringenin, a flavonoid found in citrus fruits also stimulates CCK release from STC-1 cells through TRPA1 mediated calcium signaling which was abolished in the presence of TRPA1 antagonists(Park et al. 2014). Similar reports have been published for the aglycone hesperidin and hesperetin found in oranges, stimulates CCK release from STC-1

cells *via* activation of TRPA1 channel and calcium influx mediated by TRPA1(H. Y. Kim et al. 2013). Poly-unsaturated fatty acids (PUFA) are obligatory in the mammalian diet and have many essential physiological functions inside the body. Since, TRPA1 can sense PUFA, this property of TRPA1 has opens up a new direction for its role in nutrient sensing in the intestine. Activation of TRPA1 by PUFA also stimulates the secretion of CCK (Motter & Ahern, 2012).

Cinnamon is used in traditional medicines for hundreds of years to treat post-prandial glycemia(Khan et al.. 2003; Solomon and Blannin 2009). The major anti-obesity effect of TRPA1 agonist cinnamaldehyde was found to be reduction in the ghrelin secretion in the HFD fed obese mice when given cinnamaldehyde containing diet for five weeks. Camacho *et al.* found that TRPA1 and ghrelin secreting cells co-localizes in the duodenum and they showed that cinnamaldehyde treatment upregulates the expression of TRPA1 in the MGN cell line(Camacho et al. 2015). Furthermore, cinnamaldehyde administration in HFD fed mice reduced fasting-induced hyperphagia, prevented weight gain and HFD induced inflammation(Khare et al., 2016). Even though cinnamaldehyde activates TRPA1, but these anti-obesity effects were not attributed to the direct involvement of TRPA1.

6-gingerol, the main active and pungent constituent of ginger, was used by Yang *et al.* to decipher the mechanism related with its beneficial effects in digestion. Using RIN14B and STC-1 cell lines, they showed that 6-gingerol activates TRPA1 *in-vitro* conditions and stimulates the release of 5-HT and CCK from RIN14B and STC-1 cells respectively. The use of TRPA1 specific antagonists abolishes the secretion of these hormones. They also provide the evidence for the significance of TRPA1 mediated calcium influx in the secretion of hormones from the endocrine cells of the gut(YANG et al. 2016).

Anorectic and orexigenic hormones secreted either from the brain or gastrointestinal tract regulate appetite and total dietary intake. Vomitoxin or deoxynivalenol (DON) is a mycotoxin that has been reported to suppress the food intake in mice models through the activation of TRPA1 and calcium sensing receptor (CaSR) (W. Wu et al. 2017). In earlier experiments, the same group of scientists showed that vomitoxin has anorectic effect *in-vitro* conditions as a short-term treatment of vomitoxin in STC-1 cells stimulates the secretion of GLP-1 and CCK *via* activation of CaSR and TRPA1 mediated calcium influx(Zhou & Pestka, 2015). Further to validate the same, they used mice models and found that both TRPA1 and CaSR are activated by vomitoxin, stimulated secretion of satiety hormones CCK and PYY. Also, anorectic effects of vomitoxin were abolished in the presence of TRPA1 and CaSR specific antagonists(W. Wu, Zhou et al., 2017). In addition,*in-vivo* results from another study reported increased gene expression of TRPA1 and CCK in the small intestine after 3 hours of vomitoxin administration, suggesting the anorectic effects of vomitoxin due to upregulation of CCK *via* TRPA1 (Tominaga et al. 2016).

Kim *et al* . demonstrated that methyl syringate, a pungent ingredient of *Kalopanax pictus,* is an electrophilic activator of the TRPA1 channel. They showed that through the activation of TRPA1, methyl syringate and cinnamaldehyde stimulated the secretion of PYY but not GLP-1 in ICR mice(M. J. Kim et al. 2013). TRPA1 activation potentially stimulates gut hormone secretion (Table 2). Chronic consumption of HFD downregulated the TRPA1 expression in the stomach, duodenum and ileum in mice. Reduced TRPA1 expression in HFD condition could be related with the diet induced complications like dysregulation in the secretion of gut hormones. It has been recently revealed that TRPA1 activation with allicin rich garlic extract prevented misbalance in the release pattern of the gut hormones (GLP-1, CCK, PYY and ghrelin) [unpublished data].

Hormone secretion in response to nutrients plays an important role in managing weight gain and obesity(Valassi, Scacchi et al., 2008). Being an activator of many food ingredients TRPA1 provides many advantages to be used as a therapeutic target to manage obesity and related complications.

In contrast, there are reports which stated that TRPA1 activation could lead to a stimulating effect on food intake. β-eudesmol is found in medicinal plants and activates human TRPA1 at an effective concentration (EC) of $32.5 \pm 0.38\mu$M. Oral administration of β-eudesmol to the rats increased serum ghrelin level and feed intake. But surprisingly there was no significant increase in the body weight of the rats. Ohara et al. also

demonstrated the involvement of gastric vagal nerve activity (GVNA) in the appetite stimulant. GVNA level was found to be enhanced after the β-eudesmol administration that was significantly reduced when TRPA1 antagonist HC-03001 was given prior to the β-eudesmol (Ohara et al.. 2017).

TRPA1 and Diabetes

T2DM and obesity are positively correlated with each other in terms of its prevalence and occurrence(Kahn, Hull et al., 2006). It has been observed that weight gain is a major cause in the development of T2DM in approximately 90% of the cases. In individuals with obesity, insulin resistance in liver, WAT, skeletal muscle and insulin deficiency contribute to the development of T2DM. It is generally seen that serum levels of free fatty acids (FFA) remain elevated in people with obesity both at basal level and following glucose load. These circulating FFAs are the products of excess dietary lipids and lipolysis in adipose tissues. FFAs are the key factor in the development of insulin resistance. Increased plasma FFAs by the mass action augment their cellular uptake and induction of mitochondrial β-oxidation, at the same time interfering with the enzymatic regulation of the glucose homeostasis(Boden, 2011; Roden et al., 1996; Saini, 2010). More utilization of lipids results in the accumulation of glucose or a condition known as hyperglycemia which further leads to insulin resistance. Obesity causes hypertrophy as well as hyperplasia in WAT accompanied by changes in its adipokine profile including pro-inflammatory cytokines(Esser, Legrand-Poels et al., 2014; Heilbronn & Campbell, 2008). Excessive dietary lipids get stored around the liver, skeletal muscle and pancreatic β-cells due to obesity driven dysfunctional WAT. All these factors simultaneously increase the risk for developing T2DM. Despite available treatments, use of natural compounds regulating glucose homeostasis and/or preventing obesity induced insulin resistance offers a huge advantage. During the last decade, TRPA1 is extensively explored for its role in insulin secretion and GLP-1 secretion. Hence, modulating TRPA1 could be used as a target to combat diet induced insulin resistance and related complications. In this section, we have summarized recent evidences of TRPA1 being employed as a therapeutic target to control T2DM.

5.1 TRPA1: insulin secretion

TRPA1 is expressed in the rat pancreatic islets and RINm5F cells (rat β-cell line). The 4-hydroxyalkenals like 4-hydroxynonenal (4-HNE) are commonly produced lipid peroxidation products that induce the generation of reactive oxygen species (ROS). These highly cytotoxic aldehydes accumulate in the body during T2DM. As previously reported, 4-HNE activates TRPA1 (Table 1). Application of AITC and 4-hydroxynonenal (4-HNE) induces a transient increase in calcium influx and insulin secretion in RINm5F cells(Numazawa et al., 2012). In a similar experiment, treatment with TRPA1 agonists like methylglyoxal (MG), 4-hydroxynonenal (4-HNE), prostaglandins (PGJ2) and H_2O_2 induces calcium influx and insulin secretion in cultured cells. These effects were inhibited by TRPA1 antagonists suggesting a potential role of TRPA1 channel in insulin secretion(Cao et al., 2012).

Sulphonyl urea derivative (SD) stimulates insulin release from pancreatic islets and shows anti-hyperglycemic effects. Glibenclamide is an anti-diabetic drug that belongs to the sulphonyl urea family. Glibenclamide stimulates insulin release by blocking ATP dependent potassium channels in pancreatic β-cells(Lamprianou et al., 2016). Babes*et al* . reported that this drug can activate recombinant human TRPA1 in HEK293 cells and also induces calcium influx in a subpopulation of AITC sensitive cultured mouse sensory neurons. These responses were found to be abolished both in the presence of TRPA1 antagonist HC-030031 as well as in the absence of extracellular calcium. TRPA1 antagonists abolish the insulin secretion, calcium and sodium influx suggesting a potential role of TRPA1 in secretion as well as exocytosis of insulin upon stimulation(Babes et al.2013).

Roux-en gastric bypass surgery (RYGB) helps diabetic patients to deal with insulin resistance by the up-regulation of glucose-stimulated insulin release (GSIS)(Salinari et al., 2013). RYGB also restores TRPA1 expression in diabetic GK rats and improves glucose homeostasis. It has been reported that RYGB increases the bile acid (BA) levels in both type 2 diabetic patients and diabetic rats. Bile acid stimulates the glucose stimulated insulin release by restoration of TRPA1 expression in diabetic rats after RYGB. The nuclear farnesoid X receptor (FXR), is a ligand activated transcription factor which recruits histone acetyl-transferase

steroid receptor co-activator 1 (SRC-1) to promote the acetylation of histone 3 (ACH3) at the TRPA1 promoter (Düfer et al., 2012; Renga, Mencarelli et al., 2010). Thus, BA/FXR/SRC1 axis plays an important role in the upregulation of gene expression of TRPA1 after RYGB. TRPA1 stimulates insulin secretion in diabetic β-cells and ameliorates hyperglycemia. It has been demonstrated that enhanced TRPA1 expression play an important role in glucose stimulated insulin secretion after RYGB in diabetic GK rats(Kong et al.. 2019).

Estrogen metabolites like catechol also activate TRPA1 and stimulate calcium influx as well as insulin secretion. HEK293 cells expressing TRPA1 showed increased calcium influx and inward ion current when treated with catechol: 2-hydroxyesterone where these effects were diminished in the presence of pharmacological antagonists of TRPA1. 2- and 4-hydroxylated metabolites of estradiol and estrone leads to glucose stimulated insulin secretion (GSIS) in isolated pancreatic islets and insulin-secreting INS-1 cells(Ma et al. 2019).

Due to the increasing prevalence of diabetes, incretins gain interest over the years, as these hormones help in glucose homeostasis and also insulin secretion(Chia & Egan, 2020). Incretins belong to that class of the hormones which are secreted by enteroendocrine cells upon receiving stimulus from the intestine in the form of nutrients. GLP-1 is one of the incretins which is secreted by L-type of cells present in the intestine(Lim & Brubaker, 2006). TRPA1 transcripts have been identified in the L-cells of the small intestine. Activation of TRPA1 by AITC, carvacrol and PUFA stimulate calcium influx, membrane depolarization and GLP-1 secretion in primary murine intestinal cultures and GLUTag cells(Emery et al. 2015). TRPA1 stimulated GLP-1 secretion could be used as a target to treat diabetes as the majority of the TRPA1 agonists are spices and food-based compounds. GPR119, a G-protein coupled receptor present on intestinal L cells synthesizes and secrete GLP-1. It has been reported that AS1269574, a GPR119 agonist stimulates the secretion of GLP-1 independent of GPR119. In STC-1 cells, AS1269574 mediated GLP-1 secretion through the activation of TRPA1 which was found to be abolished in the presence of TRPA1 channel blockers (Chepurny et al. 2016).

Diabetes is associated with hyperglycemia. Glucose uptake is facilitated by glucose transporters (GLUT) across the cell membranes, GLUT4 a subtype of GLUT transporter, regulates glucose level in the blood in response to insulin. Decreasing GLUT4 protein leads to hyperglycemia, therefore targeting GLUT4 translocation to the membrane could help to combat diabetes. Chronic administration of cinnamaldehyde (20mg/kg body weight) to the streptozotocin induced diabetic rats improved glycogen storage in muscles and liver. The two mechanisms involved were reported, one is upregulation of GLUT4 receptor in skeletal muscle tissue and the other is, the attenuation of phosphoenolpyruvate carboxykinase (PEPCK) enzyme in the liver and kidney(P. Anand et al. 2010). Cinnamaldehyde also stimulated insulin secretion *in-vitro* conditions (primary pancreatic islets culture) at a very high glucose concentration (10mM). Cinnamon extract lowers down circulating blood glucose levels in Db/Db mice and slows down the progress of the disease by upregulation of PPAR-γ and adiponectin. PPAR-γ and adiponectin improves blood lipid profile and increases insulin sensitivity(S. H. Kim & Choung, 2010). Also, cinnamon extract improves insulin sensitivity in the brain and improves glucose homeostasis in the HFD fed mice(Sartorius et al. 2014). Although these reports do not show the direct involvement of TRPA1 channel, but being a potent activator of TRPA1 channel, cinnamaldehyde mediated anti-diabetic effects could be further investigated for TRPA1.

Another TRPA1 agonist that has been extensively studied for the treatment of diabetes is AITC. AITC has been reported to improve insulin secretion in diabetic rats (Sahin et al., 2019). Type 2 diabetes is associated with insulin resistance. Circulating FFA diminishes insulin signaling cascade and glucose uptake. *In-vivo* study on HFD mice showed positive effects of AITC on circulating levels of blood glucose by protecting the development of insulin resistance and stimulation of insulin secretion from the pancreas. Blood glucose levels were found to be lowered along with the inhibition of lipid peroxidation (Ahn, Lee et al., 2014). TRPA1 agonist AITC has been reported to have anti-diabetic, anti-inflammatory and anti-oxidant properties. These reports do not connect all this information with TRPA1 but considering previous reports TRPA1 channel could be explored.

AMPK is known to modulate the expression of many ion channel proteins in the cell under different stress conditions. The use of AMPK activators downregulates the expression of TRPA1 on the membrane. Both

short-term topical, as well as long term systemic administration of AMPK activators, prevented mechanical allodynia in diabetic mice and expression of TRPA1 on the membrane was also normalized(S. Wang et al., 2018).

Conclusion

Obesity has been accepted as a very serious health problem which impairs the quality of life due to its association with other life-threatening diseases including type 2 diabetes, cancer, dyslipidemia and many more. Obesity is present worldwide affecting the social and economic status of both developed as well as developing countries. Health care costs associated with the treatment of obesity and related comorbidities foists an extra burden on the nation. Despite available treatments, there is a burgeoning demand for the development of new nutraceuticals with minimum side effects. TRPA1 channel has emerged as an attractive target for the prevention of obesity and associated complications. Activation of TRPA1 by a vast range of natural stimuli, its expression in the entire body (neuronal and non-neuronal tissues) and established role in the control of body weight, secretion of satiety hormones, insulin secretion, BAT thermogenesis has given a new direction to this area of research. Even though comprehensive studies have been done for TRPA1 in different aspects, some intriguing facts are yet to be discovered. The gating mechanism of TRPA1 in response to non-electrophilic activators is poorly understood. TRPA1 homologues have been reported in different mammalian species, which have different structures and activation patterns to the agonists. The development of new TRPA1 based modulators either for obesity or related complications cannot be done without coherent studies. Additionally, we still do not understand the intracellular trafficking of the TRPA1 and regulation by intracellular factors.

TRPA1 is a calcium permeable channel. From the available literature, calcium influx has been marked as a characteristic feature of TRPA1 dependent secretion of gut hormones and insulin either *in-vitro*or *in-vivo* conditions (Figure 3). Many TRPA1 agonists have been cited to prevent type 2 diabetes and insulin resistance but a little has been explored to discover the direct role of TRPA1 in these preventive effects. Undoubtedly, dietary modulation of TRPA1 in the gastrointestinal tract and pancreas has shown the potential to combat obesity and T2DM (Table 2). At the same time, it is very crucial to determine the final concentrations of these dietary agonists that could reach to the target organs harboring TRPA1. Thus, TRPA1 modifications through its natural and/or dietary agonists offer an alternative approach for the use of TRPA1 agonism to counteract obesity and associated complications.

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Figure Legends

Figure 1. Overview of human TRPA1 protein structure: *Ονλψ ονε ΤΡΠΑ1 συβυνιτ ηας βεεν ρεπρεσεντεδ, ςονταινινγ σιξ τρανσμεμβρανε δομαινς/ ηελιςες, πρε-Σ1 ηελιξ, λινκερ δομαιν, ανκψριν ρεπεατ δομαινς, ΤΡΠ λικε δομαιν ανδ β-σηεετ.*

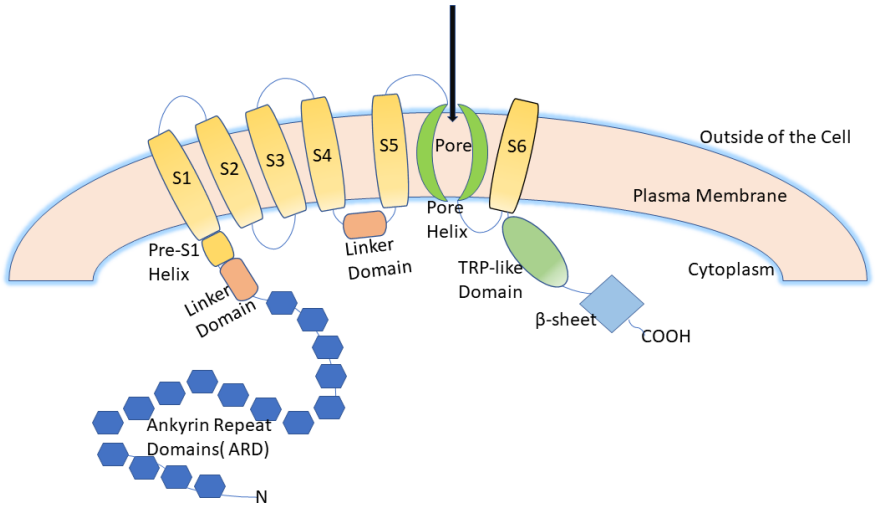
Figure 2. Expression pattern of TRPA1 in different organs

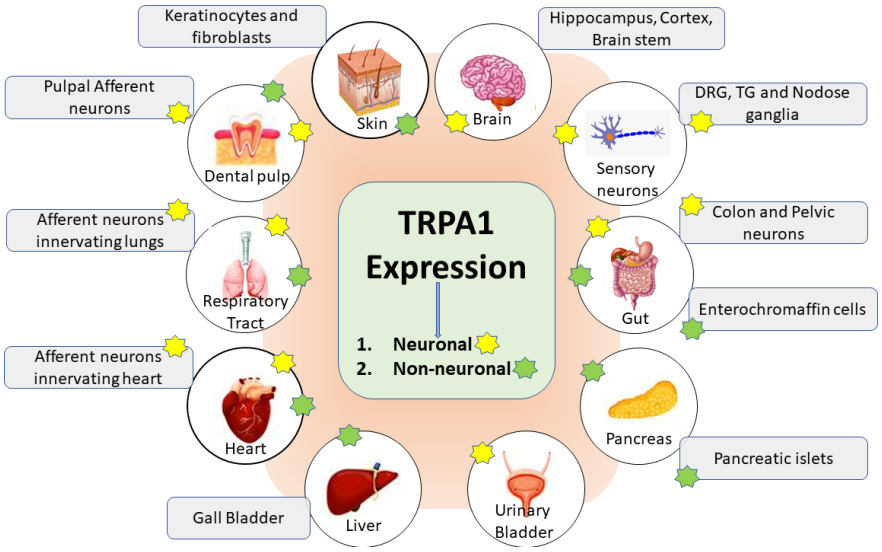
TRPA1 is expressed on sensory neurons innervating various organs including respiratory tract, heart, gastrointestinal tract, urinary bladder etc. Non-neuronal cells of many organs like enterochromaffin cells of intestine, keratinocytes. Melanocytes, pancreatic islets, gall bladder etc. also express TRPA1 on cell membrane. Representative figure showing major organs expressing TRPA1 (different colored stars have been used for the neuronal and non-neuronal expression in respective organs)

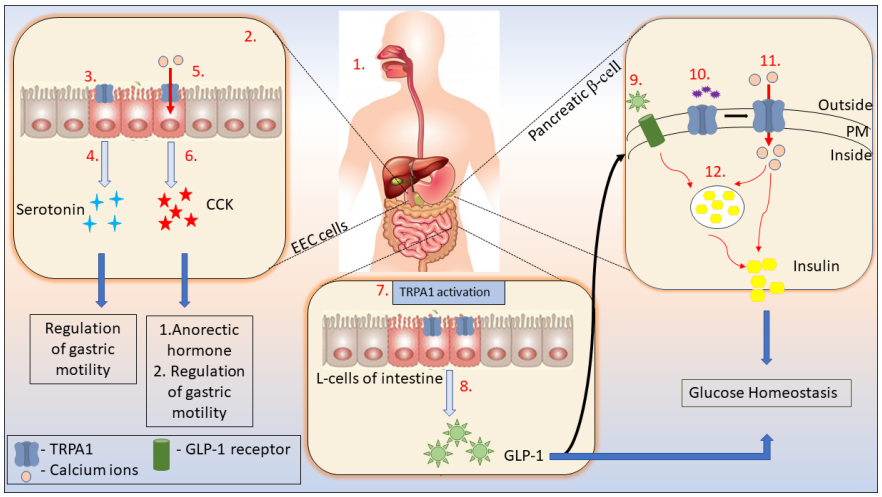
Figure 3. Significance of TRPA1 mediated calcium influx in the gut hormone and insulin secretion from the gastrointestinal tract and pancreas respectively

(1) Ινγεστιον οφ ΤΡΠΑ1 αγονιστς. (2) Ον ρεαςηινγ σμαλλ ιντεστινε, βινδινγ οφ ΤΡΠΑ1 αγονιστς το ιτς ρεςεπτορ ον εντεροςηρομαφφιν ςελλς (ΕΕ͂) (3) πρεσεντ τηρουγηουτ τηε γαστροιντεστιναλ τραστ, στιμυλατες τηε σεςρετιον οφ σεροτονιν ορ 5-ΗΤ φρομ στορεδ εσιςλες ιν τηε ΕΕ͂ (4). Σεροτονιν ρεγυλατες γαστρις μοτιλιτψ βψ εξςιτατιον οφ αριους ινπρινσις ανδ εξτρινσις νευρονς. ΤΡΠΑ1 αγονιστς ωηεν ρεαςηες δυοδενυμ, ινδυςες ςαλςιυμ ινφλυξ ινσιδε τηε ΕΕ͂ (5), ωηιςη φυρτηερ λεαδ το σεςρετιον οφ ανορεςτις ηορμονε, ͂Κ (6). Ιν ςολον, Λ ςελλς εξπρεσς ΤΡΠΑ1 (7), υπον αςτιατιον στιμυλατες σεςρετιον οφ ΓΛΠ-1 (8). ΓΛΠ-1 μαινταινς γλυςοσε ηομεοστασις βψ διφφερεντ ωαψς, ονε οφ τηε προμινεντ ταργετς οφ ΓΛΠ-1 ις πανςρεας. Βινδινγ οφ ΓΛΠ-1 το ιτς ρεςεπτορ ον β-ςελλς νοτ ονλψ στιμυλατες ινσυλιν βιοσψντηεσις (9) ανδ σεςρετιον (12) βυτ αλσο ενηανςες φορματιον οφ νεω β-ςελλς ιν πανςρεας. Ιν αδδιτιον το ΓΛΠ-1, ΤΡΠΑ1 αλσο ινςρεασες ινσυλιν σεςρετιον ια αγονιστις ιντεραστιονς (10). Υπον αςτιατιον, ςονφορματιοναλ ςηανγες ιν τηε ΤΡΠΑ1 στρυςτυρε αλλοως ςαλςιυμ ινφλυξ ιντο τηε ςελλ (11). ἄλςιυμ ιονς εσςαλατε τηε εξοςψτοσις οφ ινσυλιν (12)

** These pathways have been demonstrated in either cell line models or in-vivo models. This figure is a hypothetical representation of these pathways in human system.*







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