



Review

Sensory Pain Signals can be Modified by our Dietary Habits

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Abstract

Transient receptor potential vanilloid 1 channels (TRPV1) which are playing an important role in conduction of pain signals to dorsal root ganglion (DRG), can be interacted by many external and internal factors. Food ingredients and herbal products have a great impact on these receptors. Topical application or oral consumption of these products are effective in reducing pain signals with different mechanisms of action. TRPV1 is involved in a various processes including nociception, thermosensation and energy homeostasis. Role of capsaicin, unsaturated omega fatty acids, minerals, and herbal products in pain relief and molecular mechanisms are being discussed. However, some dietary supplementation with TRPV1 activity, such as capsaicin, show conflicting results. TRPV1 channels and their agonist elements may play a great impact in decreasing the risk of obesity and diabetes through different mechanisms including reducing inflammation. Therefore, TRPV1 could be dysregulated in obesity leading to the development of obesity, diabetes. Further, TRPV1 channels look like to be responsible in pancreatic insulin secretion. Hopefully, we could make it possible to produce natural food supplements to reduce pain by focusing on the role of TRPV1 channels. This will further help clinicians and surgeons to reduce pain post-surgical procedures just by modifying the patient's diet.

Keywords: Capsaicin, diet, pain, trpv1

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Transmitting signals from peripheral to central nervous system are essentially done by nociceptors. The mechanisms and signaling pathways might be induced by many factors such as inflammation biomarkers, molecular biochemical which might be responsible to produce acute or chronic pain. Dorsal nerve ganglia (DRG) and trigeminal ganglion are the place that peripheral and central branches meet each other where many biochemical factors would be induced by pain stimulus. The myelinated and unmyelinated fibers of nociceptors are responsible for mechanical stimulation and heat. The myelinated fibers are conducting acute pain (heat stimulation) and light touch (mechanical stimulation) while unmyelinated (called C fibers) afferents are responsible for slow and non-localized

pain.^[1] Unlike myelinated fibers, unmyelinated afferents, C fibers, are mostly show sensitivities to heat stimulations. Therefore; C fibers are those which are being stimulated by chemical factors such as capsaicin, histamine and have a major role in itching.^[2] The heterogeneity of C fibers has been described in many studies. There are some cellular receptors which are affected by neurochemicals and peptides, calcitonin-gene related peptide (CGRP), exerted by C fibers. The expression of c-Ret neurotrophin receptors causes the over production of G-protein coupled receptors and P2X₃.^[3] The other functional categorizations of nociceptors are on the basis on their channel activations such as TRPV1 (heat), TRPM8 (cold), ASICs (acid), TRPA1 (chemical).^[4]

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TRPV1 and Diabetes

Among all the mentioned nociceptor channels, the most important one is TRPV1 which contributes in many pathways. A sensor of heat over 42 °C, lipid-derived molecules, acidic environment and food bioactive components such as capsaicin are having a great impact on TRPV1 channel activation. Role of TRPV1 is not only has been described in peripheral sensory fibers but also it has a pivotal role in visceral pain modification such as pancreatitis.^[5] Moreover, reduced expression of TRPV1 can decrease weight gain and adjust glucose levels in type 2 diabetes in mice with high-fat diet. In fact, the blockage of TRPV1 might be recognized as a new target in treatment of weight gain, obesity and diabetes. TRPV1 has been found in both peripheral and central nervous system. The various situations including inflammatory factors, acidic environment, lipid-bioactive compounds, growth factors impact on the activity of TRPV1.^[6] Some studies have shown that the lack of TRPV1 receptor in mice improves pain thresholds by reducing inflammatory factors such as IL-1 β .^[7] The other role of TRPV1 is described with anandamide which is a ligand of cannabinoid receptors. Anandamide as a TRPV1 agonist might be able to modify the endo-cannabinoid activity of pain signals.^[8] The role of TRPV1 in control of weight and diabetes have been illustrated by many mechanisms such as reduction of inflammation in pancreatitis,^[9] however; this is not limited only to pancreatitis, researchers have explained the role of TRP channels in regulation of whole body metabolism.

Diet and TRP Channels

A well-known cation exchange channel with great impact in body metabolism and energy expenditure is TRPV1 activated by both endogenous and exogenous triggers such as capsaicin and endovanilloids.^[10] The beneficial effects of dietary and topical capsaicin in reducing obesity and diabetes by activation of TRPV1 have been shown in many studies.^[11, 12] The inflammatory factors such as tumor necrosis factor-alpha (TNF α), monocyte chemo-protein-1 (MCP-1), and interleukin (IL)-6 mRNA were reduced in mice fed with capsaicin supplements after ten weeks. Moreover, capsaicin diet can express the PPAR α and TRPV1 in liver and adipose tissue. In another study, only 3 weeks' consumption of %0.015 capsaicin supplement remarkably lowered the metabolic syndrome indices in mice. Interestingly, topical cream of capsaicin has had a great efficacy in reducing the fat tissue in mice fed with high fat diet. The topical use of capsaicin also reduced glucose, cholesterol levels, overexpressed PPAR α , PPAR γ , and reduced inflammatory factors such as TNF α , IL-6.^[13-15]

In addition to the effects of capsaicin on TRP channels, it

is interesting to mention the role of cinnamon that has a great impact on diabetes control and lipid profile. Cinnamon is a spice which is extracted of tree called Cinnamomun genus. There are some clinical trials which indicate that daily consumption of cinnamon for 40 days adjusted lipid profiles including cholesterol, and triglycerides as well as sharply declined glucose levels among 60 people with type 2 diabetes.^[16, 17] The mechanism of action described as activation of insulin receptors and glucose uptake by cinnamon, however; it is important to indicate the role of PPARs and AMPK in this mechanism.^[18] Cinnamaldehyde is the most crucial bioactive component of cinnamon which plays a great role as TRPV1 agonist. The other important ingredient which is common components of mustard, horseradish, and wasabi is allyl isothiocyanate (AITC).^[19] Studies have shown the regulatory effect of AITC in hyperglycemia and insulin resistance is by mitochondrial function adjustment. The improve of glucose tolerance and expression of glucose metabolism-related genes such as GLUT suggests that AITC probably activates TRPA1 with great impact on glucose uptake resulting improved impaired insulin signaling. The other study has shown that N-terminal cysteine of TRPV1 is responsible for the activation mechanisms of TRPV1.^[20, 21] Accumulating data shows the role of allicin, bioactive component of onion and garlic, in pain modification mechanism through N-terminal cysteine of TRPV1. The electrophysiological findings in DRG neurons from mice described that TRPV1 and TRPA1 are responsible for onion and garlic extract, allicin, in pain signal regulation.

For many years the biological effects of traditional plants such as Saffron have attracted scientists' attention. In addition to anti-inflammatory and anti-oxidant characteristics, saffron has antinociceptivs effects. Safranal, a bioactive component of saffron, is responsible for analgesic properties by reducing cytokines in central nervous system. Recently the role of safranal and its precursor, picrocrocin, has been identifies in activation of TRP channels. Contrary to TRPV1, the TRP ankyrin 1 (TRPA1), expressed by calcitonin gene related peptide (CGRP), has been shown to be activated by safranal, picrocrocin as well as allyl isothiocyanate (AITC) and cinnamaldehyde.^[22] Safranal stimulates the TRPA1 by binding to cysteine residue to activate the calcium channels and currents in DRG neurons. The role of TRP channels including TRPV1 and TRPA1 in migraine attacks has been recognized.^[23] There are some food ingredients and herbal extracts that can attenuate these migraine attacks, however; the mechanism of action has not been studied.^[24] The bioactive component of butterbur [*Petasites hybridus* (L.), isopetasin, has a great impact in reducing migraine signals by stimulating calcium responses and currents in trigeminal ganglion (TG) neurons and TRPA1.^[25]

Isopetasin also expressed CGRP in DRG neurons. Parthenolide, a derived product from feverfew (*Tanacetum parthenium*), abolishes the evoking signals through TRPA1 and inhibition of CGRP release in treatment of migraine attacks.^[26]

Polyunsaturated Fatty Acids and TRPV1

Omega-3 polyunsaturated fatty acids (n-3 PUFAs) are essential dietary fatty acids including eicosapentaenoic acid (EPA; 20:5 n-3), docosahexaenoic acid (DHA; 22:6 n-3), and linolenic acid (LNA; 18:3 n-3). The primary source of n-3 PUFAs are fish oils, vegetables and breast milk. DHA is highly concentrated in the brain and constitutes ~50% of membrane in the retina. The abundance of DHA in the brain suggests essential roles for this fatty acid in neuronal function.^[27] The role of n-3 PUFAs has been described in pain relief in rheumatoid arthritis, inflammatory bowel disease and dysmenorrhea.^[28]

Moreover, some studies indicate that the administration of a high n-3/n-6 PUFA ratio in mice has increased pain threshold efficiently.^[29] The mechanism of action is not clear very well, however, it is shown that the ability of n-3 PUFAs to compete with arachidonic acid for lipoxygenase is the main mechanism to reduce inflammatory factors. Although n-3 PUFAs have a great role in reduction of neuron excitability to alleviate pain signals, it is considered as a TRPV1 receptor as well. These fatty acids specially DHA has a great impact in activation of TRPV1 in a protein kinase C (PKC) dependent manner compared with EPA and linoleic acid. However, EPA significantly reduces capsaicin-induced pain in mice compared with DHA.^[30] Long chain CoAs (LC-CoA) are also activators of the TRPV1 channel which interact with C-terminal TRP domain by modulating anionic phospholipid phosphatidylinositol 4,5-bisphosphate (PIP2) residues in TRPV1. Interestingly, TRPV1 channel is modulated by LC-CoA through Ca²⁺ independently. This is a new description of TRPV1 mechanism of action by bioactive components of our diet.^[31]

Minerals and TRPV1

The health effects of Zinc have been studied in many research centers. The anti-inflammatory role of zinc and pain relief effects of zinc is being studied. One study has described that zinc can reduce pain in neuropathy after chemotherapy by paclitaxel. Interestingly, zinc can inhibit TRPV1 channels in peripheral neuropathy in mice given paclitaxel.^[32] It should be mentioned that zinc is a wound healing agent and can alleviate the pain through many mechanisms. There is a protein receptor on cell membrane, called NMDA, which shows a great sensitivity to zinc. Studies have shown that pain relief mechanism of zinc is through the inhibition of this NR2A-NMDA signal transduction.^[33] Vitamin A and its

derivatives such as retinoids which are playing a great role in cell proliferation in ophthalmic system, are vital in skin disorders and cancers. Scientists have discovered that the topical application of retinoids cause pain and hypersensitivity through the activation of TRPV1, capsaicin receptor. This indicates that TRPV1 is a target of retinoids and helps to explore the new pain-relief methods.^[34] In addition, there are some other minerals such as cadmium and copper which are interacted with TRPA1 in pulmonary sensory neurons. Transient receptor potential A1 (TRPA1) with similar structure to TRPV1 is expressed in pulmonary C-fiber afferents which is the main sensor for irritants in lung.^[35] Isothiocyanate bioactive compounds found in wasabi, horseradish and mustard owe their pungency have a great impact on TRP channels. Studies have described that topical application of mustard oil to skin causes pain and inflammation through the activation of sensory nerve endings.^[36]

In conclusion, nociception is a vital defensive mechanism to detect harmful signals resulting in pain perception. Most of TRP ion channels work as primary receptors to detect chemical, thermal, and mechanical noxious stimuli to evoke the pain and itch sensations. Among them TRPV1 channels are which including members of the vanilloid subfamily (TRPV1, TRPV3, and TRPV4). Regarding to protective mechanisms as pain and itch, there should be an inhibitory molecular mechanism activated by food ingredients targeting specifically TRP channels. By developing safe and effective TRPV1-modulating bioactive components, a beneficial diet and herbal medicine protocols on the basis on dosing strategies will be made. Despite of clinical applications of pain relief drugs which target more than one specific channel, the administration of high-potency natural bioactive components will be useful in mechanism discovery of functional-structural level.

Disclosures

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