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Review

Some like it hot: The emerging role of spicy food (capsaicin) in autoimmune diseases

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ABSTRACT

Autoimmune diseases refer to a spectrum of diseases characterized by an active immune response against the host, which frequently involves increased autoantibody production. The pathogenesis of autoimmune diseases is multifactorial and the exploitation of novel effective treatment is urgent. Capsaicin is a nutritional factor, the active component of chili peppers, which is responsible for the pungent component of chili pepper. As a stimuli, capsaicin selectively activate transient receptor potential vanilloid subfamily 1(TRPV1) and exert various biological effects. This review discusses the effect of capsaicin through its receptor on the development and modulation of autoimmune diseases, which may shed light upon potential therapies in capsaicin-targeted approaches.

Contents

1. Introduction

Chili pepper is a basic element of culinary culture consumed worldwide, especially in China, Mexico and Italy. Capsaicin, chemically (E)-N-[(4-hydroxy-3-methoxyphenyl) methyl]-8-methylnon-6-enamide, is a hydrophobic alkaloid produced by chili peppers and accounts for their spicy/pungent flavor [1]. Capsaicin has also showed beneficial roles in cardiovascular and gastrointestinal conditions, as well as in pain relief, weight loss and cancer prevention [2–10]. In a large prospective study of over 0.5 million adults from 10 geographically diverse areas across China, the habitual consumption of spicy food was found to be inversely related with total and specific mortality [11]. However, capsaicin's role in autoimmune diseases remains largely unknown. When focusing on the epidemic characteristic of the distribution of autoimmune diseases and the consumption of spicy food, one will be surprised to find that living near the equator is associated with greater intake of spicy food

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and a lower risk of having autoimmune diseases compared with living near the polar region. One possible explanation is the protective effect of ultraviolet radiation (UVR) and vitamin D production in autoimmune diseases, such as multiple sclerosis, insulin-dependent diabetes mellitus and rheumatoid arthritis [12,13]. Recently, there is an increasing evidence regarding the emerging role of capsaicin in autoimmune diseases such as autoimmune diabetes [14], rheumatoid arthritis [3] and multiple sclerosis [15].

In this paper, we will provide an overview of the recent research referring the relationship between capsaicin and autoimmune diseases and discuss the possible underlying mechanisms.

Besides all these benefits, capsaicin has long been shown to exhibit antimicrobial and anti-virulence activity [16]. A bactericidal effect has been described against *Helicobacter pylori* and *Pseudomonas aeruginosa* [17,18], and an anti-virulence activity has been demonstrated against *Vibrio cholerae*, *Staphylococcus aureus* and *Porphyromonas gingivalis* [19–21]. A recent study [22] documented the in vitro bactericidal activity of capsaicin against *Streptococcus pyogenes* (Group A streptococci, GAS), a major human pathogen, by inhibiting intracellular invasion and hemolytic activity. Such antimicrobial properties may have an important effect on the gut microbiota population in humans, but how capsaicin may affect the composition and activity of the gut microbiome has yet to be further investigated.

2. Capsaicin's receptor

Following the understanding of its biological effects, capsaicin's target receptor, transient receptor potential vanilloid subfamily member 1 (TRPV1), was discovered [23]. TRPV1 is a $Ca^{(2+)}$ permeable ion channel, highly expressed on the taste buds within the papillae of the tongue, as well as by nociceptive sensory neurons in dorsal root and trigeminal ganglia [24].

TRP channels form a superfamily of non-selective cation channels that provide cells with the information about external and internal environment. These channels participate in the sensory transduction of light, pain, touch, temperature, osmolality, taste, pheromones, acidity, inflammation, oxidation, metabolic energy and polyunsaturated fatty acids [25–33]. The TRP channel superfamily is classified into six related subfamilies: TRP cation channel subfamily C (canonical; TRPC), TRP cation channel subfamily V (vanilloid; TRPV), TRP cation channel subfamily M (melastatin; TRPM), TRP cation channel subfamily A (ankyrin; TRPA), TRP cation channel polycystin subfamily (TRPP) and TRP cation channel mucolipin subfamily (TRPML) [32]. Transient receptor potential vanilloid subfamily member 1(TRPV1) belongs to TRP V subfamily, and it is directly activated by capsaicin and high temperature (>43 °C), protons and endovanillloids [32,34].

TRPV1 is activated via phosphorylation by protein kinases, the calcium and calmodulin-dependent protein kinase II (CaMK II kinase), followed by cleavage of phosphatidylinositol 4,5-bisphosphate (PIP2) by phospholipase C. Following activation by capsaicin, TRPV1 goes into a long refractory state and thus a previously excited neuron is resistant to various stimuli [35]. The stimulation of TRPV1 leads to release of neuropeptides, including substance P and calcitonin gene-related peptide (CGRP) from sensory nerves [36]. Neuropeptides have the potential to contribute to inflammatory disease as the "neurogenic component" via a variety of mechanisms [37]. The release of neuropeptides is dependent on capsaicin concentration and also prevents the restoration of the neuropeptides by blocking axoplasmic transport of substance P and somatostatin in sensory neurons, thereby depleting neuropeptides [38]. This is thought to be the primary mechanism responsible for pain relief, which after a cascade of "de-functionalization" action is initiated in the nociceptive fibers to obtain a long term release from pain [39]. At the molecular level, this results from extracellular calcium dependent conformational changes in the receptor protein, ultimately closing the channel pore. While originally reported to serve as a pain and heat detector in the peripheral nervous system, TRPV1 has been implicated in the modulation of blood flow and osmoregulation as well as in neurotransmission and synaptic plasticity within the central nervous system. In addition to its central role in nociception, evidence is accumulating that TRPV1 contributes to a wide range of anti-inflammatory response. There is a widely distributed nerve fibers network that expresses TRPV1 in various organs, and the biological effects of capsaicinoids in different target organ or tissue are diverse.

The biological effects of capsaicin are dependent on the dose of the compound administered and the time of exposure. At present, two alternative, but not mutually exclusive, strategies are pursued to prevent TRPV1 activation: one is the use of TRPV1 agonists such as capsaicin and resiniferatoxin [40], an ultrapotent capsaicin analog to desensitize hyperactive TRPV1-expressing sensory nerves, and the other is the administration of TRPV1 antagonists for receptor blockade. High-dose capsaicin can, however, destroy TRPV1-positive neurons, especially when given to newborn animals. This protocol is used to delineate the contribution of TRPV1-expressing nerves to various biological functions [41]. Low concentrations of capsaicin are included in over-the-counter analgesic creams. High concentrations of capsaicin have been explored as treatment for neuropathic pain (e.g., Qutenza/NGX-4010), postoperative pain (e.g., Adlea; Anesiva Inc.) and cluster headaches (e.g., Civamide; Winston Laboratories) [42].

3. Roles of capsaicin receptor in immune response

Recent studies focusing on tumor immunity, allergy and inflammation have noted the immunotherapeutic effects of capsaicin. Although capsaicin's receptor was first known for its role as a molecular integration in nerve conduction, the close interplay between the peripheral nervous system and the endocrine autoimmunity renders the potential pharmacologic application of capsaicin in autoimmune diseases. TRPV1 receptors are widely expressed in both innate and adaptive immune cells in human and mammals, such as primary human T cells, murine splenic T cells and dendritic cells (DC). The inhibition of TRPV1 has been shown to regulate mitogenic T cell receptor mediated T cell activation with effector cytokines production by suppressing TNF, interleukin-2(IL-2) and interferon-gamma(IFN-γ) [43]. In experimental periodontitis, the production of TNF-α, IL-1β, IL-6, IL-12, and iNOS was suppressed after capsaicin treatment, suggesting a beneficial role of capsaicin on periodontitis [21]. Natural killer (NK) cells are an important component of the innate immune system that survey host tissues for signs of infection, transformation or stress. An impaired natural killer (NK) cell function characterized by reduced cytotoxicity effect and cytokine production was reported in gastric cancer treated with capsaicin [5]. However, other studies have shown the controversial findings about its function in cancer genesis; the ability of capsaicin treatment to suppress the survival of myeloma cells was observed, marked by reduced STAT3 phosphorylation and activation. The dephosphorylation of STAT3 led to the reduction of the Mcl-1 expression and DAMP exposure, which subsequently promote DC activation and mediate tumor cell death and autophagy [44]. The explanation to the different effects of capsaicin in cancer may lie in the dose and exposure times of capsaicin used. For example, capsaicin-induced apoptosis in gastric cancer cells required higher concentrations and longer exposure times than those required to trigger NK cell dysfunction. A more compelling evidence of capsaicin-induced immune regulation may come from the observation that DC would exert enhanced antigen presentation capacity, expression of co-stimulatory molecules and migration ability to the local lymph nodes when engaged by capsaicin [45]. Moreover, administration of capsazepine, a TRPV1 blocker, could inhibit TLR3-induced TNF-α, CXCL8 and IFN-β production in primary epithelial cells from asthmatic and chronic obstructive pulmonary disease donors [46]. A recent study has demonstrated the effect of mitochondrial TRPV1 receptors on the migration of microglia, a resident immune cell in the brain. Treatment with capsaicin induced an increase in intramitochondrial Ca2 + concentrations and mitochondrial depolarization in mice, when compared with

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