Capsaicin: A Potential Therapy Adjuvant for Intestinal Bowel Disease

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Abstract

Most of the patients with inflammatory bowel disease avoid pepper or spicy food, alleging that this condiment causes anal sensation of burning and accelerates intestinal movements. Capsaicin is the main bioactive component of peppers responsible for the pungent flavor that characterizes red peppers. Capsaicin has been related to several biological effects, including decreased body fat, antianti-inflammatory, anticarcinogenic, antioxidant activites and modulator of intestinal motility. These actions mostly are due to its role as an agonist of the transient receptor potential vanilloid 1 (TRPV1), expressed in the mesenteric nervous system and epithelial cells of the colon. Nonetheless, the anti-inflammatory action of capsaicin is also related to its role in activating the peroxisomal proliferator-activated receptor gamma (PPAR-γ). Topical capsaicin formulations are already used for pain management, but oral administration of capsaicin is rare. Here, we discuss the main actions of capsaicin that could interfere with the symptoms and severity of IBD. Although animal experiments suggest a beneficial effect of capsaicin on colitis, clinical studies exploring the potential analgesic and anti-inflammatory of capsaicin on Crohn or Ulcerative Colitis are scarce. We concluded that there is no evidence that capsaicin aggravates IBD symptoms or severity. On the opposite, experimental studies suggest that capsaicin could reduce intestinal inflammation by a mechanism that could involve not only the TRPV1 receptor but also PPAR γ. However, clinical studies are still scarce, and data regarding capsaicin concentrations, routes of administration, and long-term side-effects need to be better understood before its use.

Introduction

Inflammatory bowel diseases (IBD) comprise two disorders: Crohn's disease (CD) and ulcerative colitis (UC). The inflammatory process seen in UC extends from the rectum continually forward colon, affecting the superficial layers of the mucosa. The inflammation in CD involves all intestinal layer of any part of the gastrointestinal tract, alternating healthy and inflamed tissue in a non-contiguous pattern [1]. IBD may start at any age, being men and women equally affected with a first peak incidence between 20 to 40 years and the second peak in old age [2]. However, an increasing number of children and adolescents are also being diagnosed [1].

The etiology of IBD is not entirely understood yet. It is triggered by genetic and environmental factors that lead to disruption of the intestinal mucosa barrier with bacterial (or bacteria components) translocation, leading to exacerbated immune responses and chronic inflammation [3,4]. The most common symptoms of IBD are tiredness, abdominal pain, fever, diarrhea with blood or mucus, rectal bleeding, anemia and weight loss [5]. Extraintestinal manifestations involve the dermatologic and musculoskeletal systems [6]. Multiple sclerosis, psoriasis, rheumatoid arthritis and colon cancer are frequently associated with IBD [7,8]. Both UC and CD are mostly treated with a combination of aminosalicylates and immunosuppressants. The treatment should be maintained for life long due to frequent recurrences. The use of nutraceuticals could support conventional treatment, reducing the use of anti-inflammatory and immunosuppressants drugs and the consequent side effects [2].

Innate and adaptive immune responses are involved in the development and progression of IBD. The imbalance between regulatory T cells (Treg) and effector T cells (Th1, TH2, and TH17) is related to the development of UC and CD [9,10]. Pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1β, IL-6, IL-17A, and interferon (INF)-γ play essential roles in the control of intestinal inflammation and clinical symptoms of IBD. Interleukin (IL)-1β increases the recruitment of granulocytes and activation of innate lymphoid cells (ILCs), participating in the initiation of the colon

inflammation [4]. IL-23-responsive ILCs are responsible for intestinal inflammation through secretion of IL-17A and INF-γ, in addition to the recruitment of inflammatory cells [11]. On the other hand, the presence of anti-inflammatory cytokines such as IL-10, IL-37, and transforming growth factor (TGF)-β, are involved with the control of disease progression [12].

Pain is a recurrent IBD manifestation, which is present in more than 80% of patients [5]. The hyperalgesic state in the colon is initiated by the release of cytokines and other inflammatory mediators, such as serotonin, bradykinin, prostaglandins that activates sensory neurons [13]. One of the peripheral mechanosensors in afferent neuronal fibers is the transient receptor potential vanilloid 1 (TRPV1). TRPV1 is an ionic channel that permeates sodium and, preferentially, calcium (Ca^{2+}). It is expressed in several organs, including the mesenteric nervous system and involved in intestinal motility, visceral nociceptive behavior, and intestinal hyperalgesia [14,15]. The role of TRPV1 in IBD-related pain is reinforced by studies showing that TRPV1 inhibitors block the hyperalgesia related to colon inflammation. Moreover, the hypersensitivity related to intestinal distension and with inflammatory mediator's release is absent in TRPV1-deficient (KO) mice [16,17]. One of the TRPV1 natural binders is the capsaicin, making this dietary component a potential adjuvant in IBD treatment.

Pepper, Capsaicin, and IBD

Pepper, together with foods rich in fiber, is the most cited avoided foods for IBD active and in remission due to the association of such condiment with burning sensation and increased bowel movement [18].

Capsaicin (trans-8-methyl-N-vanillil-6-Nonenamide) and dihydrocapsaicin are the main capsaicinoids from peppers (*Capsicum genus*), responsible for the pungent flavor that characterize red peppers. Capsaicin, an alkaloid highly volatile and hydrophobic, is the main bioactive and strongest capsaicinoid [19,20]. The content of capsaicinoids in peppers is about 0.1 to 2.5 mg/g pepper and the consumption of capsaicin in the human diet is estimated at 0.5 to 4 mg/kg/day [21]. The Scoville organoleptic test is used to measure the degree of the pungency of several peppers (Figure 1).

Studies in rats showed that the absorption of

Figure 1. Scoville Scale of Pungency [58].
The pungency of the peppers is described according to the Scoville classification and measured by the Scoville Heat Units (SHU). Capsaicin is the main bioactive component of peppers responsible for the pungent flavor and received the highest SHU.

capsaicin (isolated) occurs mainly in the proximal portion of the gastrointestinal tract. Following intragastric administration, approximately one-third to one half of the capsaicin dose was absorbed from the stomach. The total intestinal absorption amounted to almost 90% [22]. After absorption, capsaicin is passively absorbed and metabolized in the liver by cytochrome P450 system, generating metabolites such as vaniline, vanillamine, vanyl alcohol [23]. Nonetheless, none of the capsaicin metabolites presented metabolic activity [24].

The amount of capsaicin reaching colon to be absorbed is not well known. It is possible that pure capsaicin has a faster and more proximal absorption than capsaicin contained in the spicy foods. It is well known that interactions with other food components such as dietary fibers can slow the absorption rate of some nutrients. In this way, a more significant portion of capsaicin from natural food could reach the colon compared to pure capsaicin. Some individuals allege that capsaicin containing foods induce an anal sensation of burning, suggesting that capsaicin reaches the distal parts of the colon. Nonetheless, studies with healthy individuals receiving capsaicin capsules showed that burning sensation during bowel movements was not related during the experiment [25].

Capsaicin has been related to several biological effects, including reduction of body fat [26–28], anti-inflammatory, anticarcinogenic, antioxidant activites and modulator of intestinal motility [29-35]. Most of the capsaicin actions are due to its role as TRPV1 agonist. TRPV1 can be activated by acidity and high temperatures and is described as a molecular integrator of chemical and physical stimuli that provoke pain. In the inflammatory process, the stimulation of sensory neurons leads to a response in peripheral tissues and transmission of nociception to the central nervous system. In this context, TRPV1 mediates the transmission of sensory neuron signaling involved in thermal hyperalgesia and visceral sensitivity. In the human colon, TRPV1 is overexpressed in the epithelial

cells and afferent nerves during inflammation [36].

TRPV1 activation leads to the release by sensory fibers of neuropeptides such as substance P (SP) and the calcitonin gene-related peptide (CGRP). These neuropeptides, besides their vasodilator effects, drive the transmission of nociception in the colonic mucosa. In this way, activation of TRPV1 contributes to the generation of inflammatory responses through the recruitment and migration of leukocytes to the site of inflammation, a process that is accompanied by visceral hypersensitivity [37,38].

The transient activation of TRPV1 leads to the influx of calcium ions, leading to the membrane depolarization that results in an action potential that propagates the signaling to the brain. However, when a stable and persistent agonist, such as capsaicin, is present, TRPV1 significantly increases the influx of calcium to the intracellular environment of sensitive fibers. Organelles expressing TRPV1 also release calcium into the intracellular environment. The persistently elevated levels of intracellular calcium cause dysfunctionality of nerve fibers due to temporary loss of membrane potential. In this way, chronic capsaicin exposition results in inhibition of pain transmission by inducing persistent calcium influx and nerve fiber dysfunctionality. Capsaicin also downregulates the synthesis, storage, transport, and release of SP and CGRP, both messengers of peripheral pain impulses to the central nervous system (Figure 2). The depletion of SP in nerve terminals reduces or blocks the propagation of pain impulses toward the brain [31]. In summary, although in short-term capsaicin can excite afferent neurons and induce burn sensation (by stimulating TRPV1), chronic exposure causes a block of sensory neurons, attenuating the noxious stimuli [25].

Some studies have shown that TRPV1 channels are involved in the induction and progression of colitis in humans and experimental models [39–41]. However, the participation of TRPV1 channels in inflammatory bowel diseases is still controversial, showing evidence of pro-inflammatory or anti-inflammatory stimuli [42–45].

Utsumi et al. (2018) investigated the contributions of TRPV1 and TRPA1 in a model of sodium dextran sulfate (DSS) induced colitis. They observed that pretreatment with high doses of capsaicin (100 mg/kg),

worsened rectal bleeding, and other inflammatory signs of colitis. In agreement, DSS-induced colitis in TRPV1 KO mice was less intense than in wild-type controls, suggesting that TRPV1 is associated for the colitis progression [46].

However, previous studies of Massa and colleagues showed that colitis induced by dinitrobenzene sulfonic acid was aggravated in TRPV1 KO mice [36], suggesting that these receptors could be protective against colon inflammation. Studies with sensory deafferentation induced by high doses capsaicin also exacerbated the inflammation in trinitrobenzene sulfonic acid - induced colitis [47]. In contrast with high doses, chronic administration of lower doses of capsaicin attenuated intestinal inflammation in several studies [48–50].

Few studies have evaluated the role of TRPV receptors in human colitis. A study comparing colon biopsies of patients with active IBD and healthy controls showed that TRPV1 was increased in IBD patients. TRPV1 was also highly expressed in infiltrating inflammatory cells of patients with active disease. Nonetheless, TRPV1 expression was not associated with the disease severity [51]. Another clinical study evaluated the expression of TRPV1 to TRPV4 in colonic mucosa biopsies of patients with UC or healthy controls [52]. Interestingly, unlike the previous study, patients with UC had a lower expression of TRPV1 channels in colon epithelial cells, suggesting different associations between TRPV1 and colon inflammation. Once again, TRPV1 expression was not associated with IBD clinical manifestation or with the disease severity [52].

The reduction of proinflammatory cytokines, chemokines, and adhesion molecules related to capsaicin activity seem to involve pathways not mediated by TRPV1. Capsaicin is also an agonist of the peroxisome proliferator-activated receptor (PPAR), especially of PPAR-γ [14,15,19,53,54]. PPAR-γ is part of the nuclear hormone receptor superfamily and expressed in epithelial cells, macrophages and lymphocytes, and other immune cells and plays an essential role in the homeostasis of the intestinal mucosa [15]. PPAR γ regulates colon inflammation, as
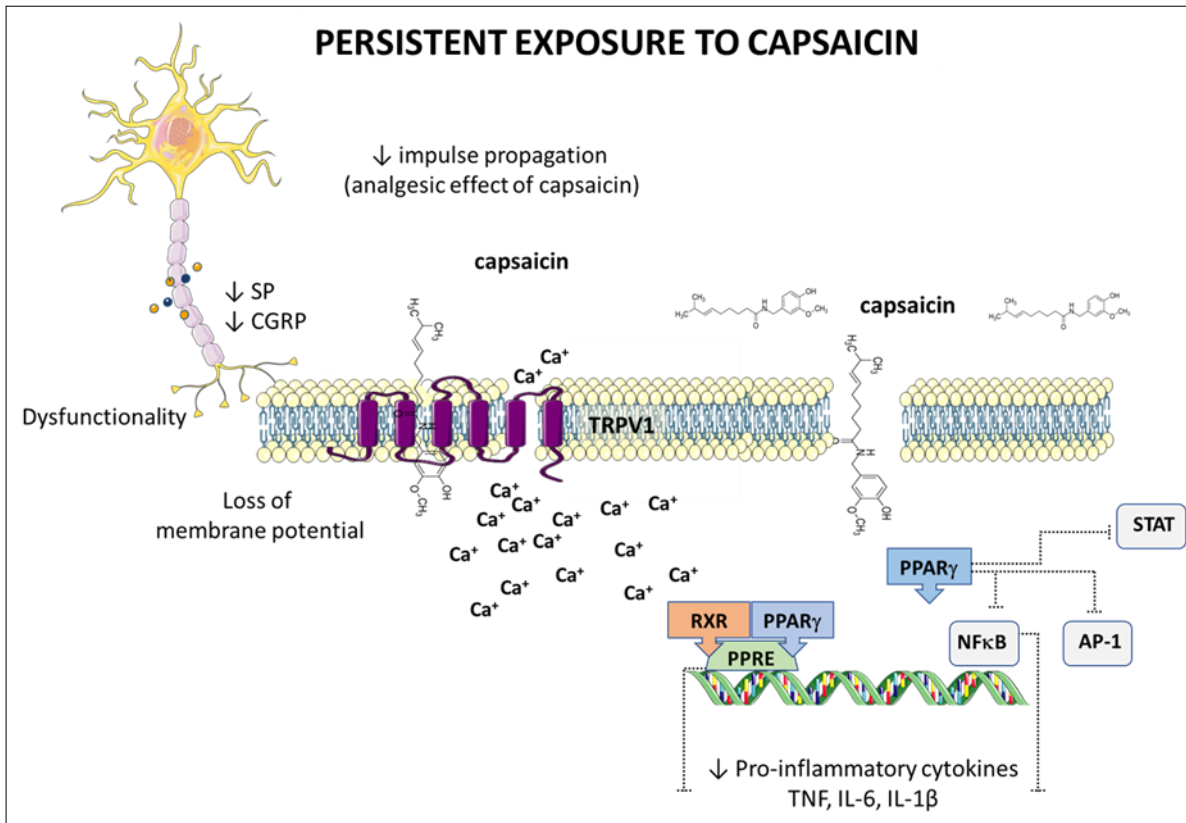
Figure 2. The proposed mechanism for analytical and anti-inflammatory actions of capsaicin in the colon. Capsaicin is a natural agonist of transient vaniloid receptor potential 1 (TRPV1). TRPV1, when activated, leads to the influx of calcium ions, leading to membrane depolarization that results in a potential action that propagates signaling to the brain. However, when a stable and persistent agonist such as capsaicin is present, persistently high intracellular calcium levels cause afferent nerve fiber dysfunction due to loss of membrane potential, inhibiting pain signal spread. Capsaicin also decreases the release of the P component and calcitonin gene-related peptide (CGRP), messengers of peripheral pain impulses in the central nervous system. Capsaicin is also a peroxisome proliferator-activated receptor (PPAR-γ) agonist that regulates inflammation of the colon. When activated, PPAR-γ binds to other nuclear receptors, such as retinoid receptor X (RXR), forming a heterodimer that in turn binds PPAR response elements (PPRE) in DNA. As a result, a protein expression encoded by the target gene will be regulated up or down. PPAR-γ also regulates gene expression by interacting with other transcription factors, such as activating protein (AP) -1, signal transducers and transcription activators (STAT), and nuclear kappa factor B (NF-κB). rules the proinflammatory gene expression.

demonstrated by animal and clinical studies [55]. To exert its action, PPAR-γ binds another nuclear receptor such as retinoid X receptor (RXR)-α, forming a heterodimer that binds to PPAR response elements (PPRE) in DNA [53,56]. As a result of PPAR γ action, the expression of proteins codified by the target genes will be up or downregulated [57]. PPAR-γ can also regulate gene expression by interacting with other transcription factors such as activator protein (AP)-1, STAT (signal transducers and activators of transcription), and NF-κB, all factors that also regulate gene expression [57] (Figure 2).

Although there are no specific studies with IBD patients or colitis models, the participation of PPARγ in the capsaicin actions was confirmed by studies with macrophages cell line (RAW) that do not express TRPV1. In this cell line, capsaicin inhibited the lipopolysaccharide (LPS) induced production of pro-inflammatory cytokines (TNF, IL-6, and IL-1β). The mechanism was dependent on PPARγ since a PPARγ agonist intensified the cytokine inhibition, and PPARγ antagonist reverts the inhibition caused by capsaicin [53]. The anti-inflammatory effect of capsaicin is possibly the consequence of PPARγ interaction with the transcription factor NF-κB. The NF-κB is closely related to the production of inflammatory cytokines, and it is the primary target for PPAR-γ to suppress inflammatory cytokine production [57] (Figure 2).

In conclusion, studies suggest that capsaicin containing foods unlikely aggravate the symptoms or the severity of inflammatory bowel diseases. On the opposite, some studies in animal models show promising results with the use of capsaicin in the control of intestinal inflammation by a mechanism that could involve not only the TRPV1 receptor but also PPARγ. However, clinical studies are still scarce, and data regarding capsaicin concentrations, routes of administration, and long-term side-effects need to be better understood before its use.

Acknowledgments

Conflict of Interest

The authors declare no conflict of interest.

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