Bulgarian Chemical Communications, Volume 57, Special Issue A (pp. 101-104) 2025 DOI: 10.34049/bcc.57.A.MU11

Gastroprotective action of capsaicin: a mini-review

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Received: September 03, 2024; Revised: February 04, 2025

Capsaicin is a pungent ingredient of chilli peppers that triggers the nociceptive pain pathway by activating the transient receptor potential cation channel subfamily V member 1 (TRPV1) receptor. There are stereotypes which claim that capsaicin is one of the phytochemicals that cause gastric injuries. This study aims to explore the recently published research data about the beneficial and protective effects of capsaicin on the gastric mucosa. Research papers and reviews from the period 2005-2024 were thoroughly examined in databases PubMed and Google Scholar. Keywords "gastroprotection" and "capsaicin" were used to identify the articles, directly associated with a gastroprotective effect of capsaicin, including preclinical experiments with animals, and human studies. As a result, the seven main possible mechanisms of its gastroprotective action were reviewed and summarised. Capsaicin leads to a dose-dependent decrease in basal acid output (BAO) and the concentration of ions in the gastric juice also decreases (except for Na^+). Gastric transmucosal potential difference (GTPD) is increased significantly, even after ethanol administration. Indomethacin-induced gastric bleeding is prevented by capsaicin. It also shows anti-inflammatory properties and reduces oxidative stress. Capsaicin-sensitive nerve endings have an important role in gastroprotection: they release calcitonin gene-related peptide (CGRP) or other vasodilators which enhance the microcirculation. The hyperaemic response plays a huge part in ulcer healing. Moderately spicy foods containing low concentrations of capsaicin protect against injurious substances and prevent gastric mucosal damage by stimulating sensory neurons. The secreted neurotransmitters provide gastroprotection by enhancing the blood flow.

Keywords: capsaicin, gastroprotection, capsaicin-sensitive nerve endings

INTRODUCTION

Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is the component of chilli peppers, responsible for their pungency. It is not distributed evenly inside the chilli pepper: higher concentrations were found in the inner white flesh around the seeds (placenta). In order to cause a spicy sensation, capsaicin excites afferent nociceptive neurons by changing their membrane permeability. All this is possible due to the activation of the transient receptor potential cation channel subfamily V member 1 (TRPV1) receptor, a tetrameric structure which allows the influx of sodium and calcium ions [1]. Calcium influx causes mitochondrial function loss and makes the nerve fibers inoperant. The production of mediators from the fibers decreases. One of these mediators is the potent local pain mediator: the substance P [2]. Other activators of the TRPV1 receptor are low extracellular pH, divalent cations (Mg^{2+}, Ba^{2+}), noxious heat, pain-producing exogenous and endogenous substances [1]. The sensation that capsaicin brings is deliberately sought by many people. Spicy foods are a popular staple for many cuisines across the globe. A common belief claims that excessive consumption of chilli peppers has an evident role in gastric ulceration. The main factors implicated in the causation of ulcers are increased acid secretion, abuse of non-steroid anti-inflammatory drugs (NSAIDs) and ethanol, reduced blood flow in the region of the gastric mucosa [3]. Human interventional studies and preclinical experiments with animals have come to controversial conclusions about the harmful effect of capsaicin on the stomach. Few properties of capsaicin, which break all stereotypes, associated with the formation of ulcers, have been discovered.

Our study aims to explore the main mechanisms of the beneficial and protective effects of capsaicin on the gastric mucosa.

MATERIALS AND METHODS

In order to gather all articles, directly corresponding to the topic, databases PubMed and Google Scholar were used. A period of 2004 – 2025 was set to identify the more recent research papers. Inclusion criterion was the keywords "capsaicin" or "gastroprotection" in the title. Seventeen manuscripts were thoroughly reviewed and many

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experiments both on humans and rodents with low concentrations of capsaicin were explored.

RESULTS AND DISCUSSION

Decrease in basal acid output (BAO)

Gastric juice is produced by gastric glands in the stomach mucosa, containing different types of cells. To notice changes in acid secretion, Mozsik *et al.* [4] suctioned gastric juice every 15 min for 1 hour (basal acid output, BAO) and inserted intragastrically small doses of capsaicin (100-800 μg), dissolved in 100 ml of saline solution. The change in BAO (measured in mEq/h) was dose-dependent and the median effective dose 50 (ED50) value was around 400 μg. A dose of 100 μg capsaicin is responsible for 1.1 mEq/h BAO, while 800 μg for 0.2 mEq/h. Decrease in acid output protects the lining of the digestive tract and prevents ulceration. It was proven that electrical stimulation of the vagal nerve causes maximal secretion. The output (after vagal stimulation and capsaicin application) decreased by 28.1% at 100 mg/ml and by 34.8% at 500 mg/ml. Decrease in gastric juice secretion is explained by H^+ back-diffusion [4-7].

Change in gastric juice composition

Application of capsaicin changes the concentration of different ions and proteins, secreted from the gastric glands [4]. H^+, K^+, Ca^{2+}, Mg^{2+} levels decrease, whereas Na^+ and albumin levels increase. The decrease is associated with the decline in hydrochloric acid secretion. Concentration of H^+ without pretreatment with capsaicin is around 43±3 mEq/L and changes to 25±1 mEq/L after capsaicin is applied. For K^+ the value without capsaicin is 13±1 mEq/L and lowers to 8±0, 6mEq/L. Ca^{2+} goes from 0.98±0.02 to 0.88±0.01. The concentrations of these three ions are measured by photoelectric flame photometry [4]. The rise in Na^+ levels is remarkable: 73±4 mEq/L turns into 89±2 mEq/L after administration of the pungent ingredient. All these changes are statistically significant and have a p value <0.001 [4]. Albumin is the protein component of the gastric juice, found in small amounts. Capsaicin usually increases albumin levels from 1.24 ± 0.001 g/L to 1.63 ± 0.02 g/L [6, 7]. Variations in the "parietal" (Cl^- linked to H^+) and "non-parietal" (Cl^- linked to Na^+) components of the gastric juice can be identified after measurement of cation concentrations and Cl^-, a principle known as Hollander's method. Due to the increase in H^+ back diffusion, a notable decline in the "parietal" element is noticed, leading to elevation in the "non-parietal" (a buffering part, which can't be produced in passive metabolic processes) [6, 7].

Effect on the gastric transmucosal potential difference (GTPD)

Gastric transmucosal potential difference is generated due to the ion transportation through the gastric mucosa and its electrical resistance. The gastric mucosal barrier plays an important role in prevention of damage to the stomach lining. Epithelial cells on the surface are part of the barrier due to their ability to transport hydrogen and chloride ions out of the mucosa and sodium ions into the plasma. Many factors destroy the gastric barrier: ethanol, NSAIDs, bile salts [8]. The destruction is followed by H^+ back-diffusion and a decline in potential difference. Capsaicin has the ability to increase GTPD dose-dependently. GTPD is measured endoscopically with one electrode passed through the biopsy force channel of the gastroscope and the other positioned on the forearm. The noted increase reaches maximum within 3-5 min [4, 6, 7].

Ethanol has the ability to induce changes in GTPD. In an experimental study [4], ethanol was administered intragastrically through the biopsy channel of a gastroscope with and without capsaicin. On its own, the alcohol caused a significant decrease in GTPD (Δ 25 (−mV)), which was prevented with capsaicin [4, 6]. Early studies [9] have come to the conclusion that ethanol causes erythema in the gastric mucosa. Reduction in blood flow leads to swift destruction of the stomach walls. This reduction is characterized by venule constriction, accompanied by arteriolar dilatation. Application of capsaicin further dilated the arterioles but also blocked the ethanol-induced constriction by release of calcitonin gene-related peptide [9, 15-17]. Maximum dilatation of the arterioles after capsaicin was reached within 3 min [9]. Ethanol can also induce oxidative damage in rats, but capsaicin manages to inhibit the lipid peroxidation and myeloperoxidase activity, a marker enzyme, released by polymorphonuclear leukocytes (PMNs) [10].

Antioxidant and anti-inflammatory properties

Indomethacin is a nonsteroidal anti-inflammatory drug used to treat moderately acute pain, which is known to change the mitochondrial structure in gastric mucosal cells. Mitochondrial dysfunction is followed by an increase in reactive oxygen species. Superoxide inactivates the enzyme aconitase, iron is released and hydroxyl radical (·OH) is produced. ·OH leads to apoptosis and gastric injuries [11]. The microbleeding after intake of indomethacin can be determined by calculating the concentration of hemoglobin in the gastric juice (Fisher and Hunt method). Before application of indomethacin blood

losing was around 2.0 ± 0.02 mL/day for a period of 1 day. After the NSAID was given, the baseline increased to 8.1 ± 0.02 mL/day. Orally given capsaicin in concentrations of 200, 400 and 800 μg prevented the microbleeding and proved the gastroprotective effect of chillies by inhibition of the COX enzymes [4, 6, 7].

Ethanol consumption may lead to serious health conditions such as gastritis, gastric ulcer, gastric cancer. It damages the gastric mucosa, which results in pro-inflammatory cytokine imbalance. Neutrophils and reactive oxygen species (ROS) accumulate in the site of the damage. Experiments *in vitro* [12] show that capsaicin limits the transcription of chemokine receptor 4 (CCR4) which plays the role of a marker for oxidative damage. Src and p47phox expression is also suppressed. Src (a tyrosine protein kinase) regulates the activity of NADPH oxidase, which is a source of ROS and thus acts as a modulator of oxidative stress. P47phox is part of NADPH oxidase, which needs serine phosphorylation in order for the enzyme to be activated. The gastroprotective effect of capsaicin is associated with reduced ROS generation due to suppression of NADPH oxidation [12]. Another damage to the gastric mucosa, caused by ethanol, is increased lipid peroxidation, an index for which is the concentration of malondialdehyde (MDA). Capsaicin inhibits this process by scavenging ROS, responsible for the peroxidation. The inhibition may occur at the level of the membrane by altering oxidoreductase activity. Ethanol induces the myeloperoxidase activity, but a significant decrease is noted (4.6%, 54.1%, 59.4%) with capsaicin doses of 0.5, 5.0, 10 mg/kg BW. The inhibited lipid peroxidation limits the number of PMNs at the site of the damage. Inflammatory processes are associated with the expression of the enzyme COX-2, related to prostaglandins production (arachidonic acid pathway). Capsaicin prevents the ethanol-stimulated expression of the enzyme, again proving its anti-inflammatory properties [10]. Treatment with capsaicin lowers mRNA expression levels not only of COX-2 but other proinflammatory molecules such as TNF-α, IL-1β, IL-6 [13]. Capsaicin also inhibits the production of IL-8 from *Helicobacter pylori* infected gastric epithelial cells. Not only was the secretion of the protein affected but also the IL-8 mRNA expression, which decreased. This interleukin brings neutrophils to the inflamed mucosa. *H. pylori* is a gram-negative bacterium which causes serious harm to the gastric mucosa. In response to the bacterium, gastric cells up-regulate the expression of genes modulated by nuclear factor kappa B (NF-κB), a dimeric transcription factor. The dimers are in an inactive state and are located in the cytoplasm, held by inhibitory kappa B (IκB) proteins. Activation of the factor happens after phosphorylation of IκB and a following proteolysis, mediated by ubiquitin, which sets the dimers free and they translocate in the nucleus. NF-κB is a regulatory element for IL-8 expression so it comes as no surprise that capsaicin suppressed the activation of NF-κB, induced by the bacterium [14].

Effect on ulcer healing

The first layer of protection in the stomach consists of the mucosa-bicarbonate-phospholipid barrier and the epithelial cells, connected with tight and gap junctions. NSAIDs, ethanol and other substances damage the epithelial barrier, which results in an increased H^+ back-diffusion [15]. The barrier's main function is to prevent the contact between hydrochloric acid in the lumen and the gastric mucosa. Without it, serious conditions, such as gastric ulcers, may develop. Another way, in which the mucosa may keep its integrity, is with the help of a neurotransmitter, secreted from capsaicin-sensitive sensory nerves (after activation of the TRPV1 receptor) – calcitonin gene-related protein (CGRP). CGRP is mainly synthesized in the dorsal root ganglion and is transported to the peripheral nerve endings. The main physiological effects of the peptide are vasorelaxation (it is known as the most potent vasodilator) and inotropic actions. There is also evidence that CGRP inhibits gastric acid secretion (in a rat experimental model an estimated 63–78 % inhibition was noticed [16]). CGRP influences the blood flow through adenosine triphosphate sensitive potassium channels (KATP channels), the increase in blood flow helps with the repairment of the gastric mucosa and protects against ulcerations. The peptide is also known to increase nitric oxide (NO) by influencing the inhibitor of nitric oxide synthase: asymmetric dimethylarginine, ADMA [16]. The subserosal injection of acetic acid in the stomach of rats, which leads to chronic gastric ulcers, was used to explore the importance of sensory neurons in gastroprotection. 24 h after the injection necrosis is present and after 1 week the condition reaches a "chronic" state. Daily consumption of capsaicin managed to decrease the size of the ulcer a week later. Rats with ablated sensory nerves showed an increase in the size of the damaged area [17].

CONCLUSIONS

Spicy foods containing low concentrations of capsaicin (50 μg – 800 μg) have the ability to provide gastroprotection. The effect of injurious substances

such as ethanol and indomethacin can be significantly reduced with the activation of sensory neurons and the TRPV1 receptor. The secreted neurotransmitters enhance the blood flow and thus repair damages to the gastric mucosa. Reduction of oxidative stress turns capsaicin into an underrated gastroprotective drug.

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