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Research Progress on Effect of Capsaicin on Pathogenesis of Gastric Disease

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Abstract

Capsaicin is the most important active ingredient in pepper. In recent years, the research on capsaicin has become a hot topic, and it has been found to have anti-inflammatory, analgesic, antioxidant, anti-tumor and other effects. The stomach is the most direct organ for the human body to accept pepper and has the longest contact time. The effect of capsaicin on it is self-evident. This article reviews the effect of capsaicin on the mechanism of gastric disease, and discusses the positive and negative effects of capsaicin in the development of gastric diseases. In order to provide a reference for future research on avoiding the side effects of capsaicin and exerting the positive therapeutic effect of capsaicin.

Keywords

CAP; Gastric Mucosa; tRPV1 ; Gastritis; Gastric Cancer.

1. Introduction

Pepper is a widely consumed spice. Capsaicin (CAP) is the main chemical component that causes the pungent taste in pepper fruit. It is the main reason for the spicy taste and is produced by pepper in response to herbivores and fungi. Studies [1] have shown that there is a transient receptor potential vanilloid 1 (TRPV1) ion channel protein in the human body, which is highly sensitive to CAP.CAP can act by selectively stimulating TRPV1 on the cell membrane. The cells with TRPV1 are distributed in the gastric mucosa, submucosal perivascular, myenteric plexus and smooth muscle layer, and are widely expressed in the gastrointestinal tract. After CAP stimulation, they can release a variety of neuropeptides to exert anti-inflammatory, analgesic, anti-oxidation, vasodilation, protection of gastric mucosa and anti-tumor effects [2-5]. In recent years, more and more scholars have made great progress in studying the effect of CAP on the pathogenesis of gastric diseases. Domestic and foreign studies have found that appropriate amount of CAP may have a positive therapeutic effect on gastric diseases, but the same excessive CAP will also have a negative effect on gastric diseases. Therefore, the effect of CAP on gastric diseases has become a controversial hot topic. Therefore, the author reviews the positive and negative effects of CAP on the pathogenesis of many gastric diseases.

2. CAP and gastric mucosa

The gastric mucosa is the mucosa inside the gastric cavity, which belongs to the innermost layer of the gastric wall. It is normally pale pink. The common types of gastritis, gastric ulcer and gastric cancer are mainly gastric mucosal lesions. First of all, there is a very tight barrier between the gastric cavity and the gastric mucosal gap. This barrier is called the gastric mucosal barrier. It is maintained by many physical, chemical and physiological factors. The gastric mucosal barrier can prevent H + in the gastric cavity from invading the gastric mucosa, thereby

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protecting the gastric mucosa. When stimulated by certain factors, the gastric mucosal barrier will be destroyed, which in turn causes H + erosion in the gastric cavity to destroy the gastric mucosa, causing gastric mucosal swelling and bleeding, causing a series of gastric diseases [6]. Secondly, in addition to the protective effect of gastric mucosal barrier, many other endogenous substances also help to protect gastric mucosa from damage caused by external stimulation. Among them, calcitonin gene-related peptide (CGRP), as a neurotransmitter, is widely distributed in the gastrointestinal tract. It is the main neurotransmitter of the afferent nerve of the spinal cord in the stomach and has been proved to be involved in protecting the gastric mucosa from various stimuli. It mainly protects the gastric mucosa by inhibiting gastric acid secretion, increasing gastric mucosal blood flow, anti-inflammatory, anti-apoptotic and other mechanisms, and is a recognized gastric mucosal protective substance [7]. However, studies [8] have shown that when TRPV1 receptor is stimulated by CAP, a large amount of CGRP can be released, and CGRP is the main transmitter released by TRPV1 receptor. Therefore, it can be said that CAP is indirectly involved in the protection of gastric mucosa.Yang Feng [9] found that after 4 weeks of intragastric administration of CAP in rats, the level of CGRP in rat blood was up-regulated, and the level of CGRP in gastric cavity was also significantly increased, and it could prevent gastric mucosal injury caused by ischemia-reperfusion, which proved that CAP could protect gastric mucosa by up-regulating the expression of CGRP in stomach. In addition to the above-mentioned ischemia-reperfusion, the damage of gastric mucosa is more caused by chemical factors (non-steroidal anti-inflammatory drugs and alcohol, etc.) on the gastric mucosal barrier. Mózsik Gyula [10] 178 subjects were selected and given CAP-indomethacin, CAP-ethanol, indomethacin, and ethanol to induce gastric mucosal microbleeds and observe the gastric secretion response. The experiment found that the degree of gastric mucosal injury in the latter two groups was much larger than that in the first two groups, and it was found that CAP also had an inhibitory effect on gastric mucosal microbleeds caused by indomethacin. Therefore, CAP can be used as a new oral gastric protective agent for high-risk groups that need long-term use of indomethacin or alcoholism. The study also pointed out that CAP can not only prevent gastric mucosal injury preventively. It is also suitable for repair after injury. It is not difficult to see the positive role of CAP in maintaining the integrity of gastric mucosa.

3. CAP and gastritis

Gastritis is a kind of gastric mucosal inflammation caused by various reasons, which is one of the most common digestive diseases. Clinically, it is often divided into acute gastritis and chronic gastritis, and the main cause of the disease is long-term use of non-steroidal anti-inflammatory drugs ; followed by Helicobacter pylori (Helicobocton Pyloni, HP) infection and increased activity of acid-secreting cells [11]. However, inflammation caused by any reason is inseparable from the chemotaxis of inflammatory factors, resulting in the imbalance of the body 's immune system, which in turn causes the imbalance of the body 's internal environment to produce pathological reactions [12].Therefore, these inflammatory factors play an important role in the development of gastritis. Many studies at home and abroad have confirmed that the appropriate amount of CAP can inhibit the release of inflammatory factors, which has a positive effect on the development and prevention of gastritis. Mendivil Edgar J et al. [13] found that in the model group of long-term (8 weeks) chronic administration of CAP in mice, the levels of TNF-α, IL-1β, IL-6 and COX-2 mRNA in mice did not increase, but decreased. In the model group of 2 weeks of gastritis induced by acetylsalicylic acid and 2 weeks of CAP, the gene expression of pro-inflammatory molecules in mice was significantly down-regulated, and even reached a level similar to that of healthy control animals, which indicated that CAP not only did not induce gastritis, but also reduced the expression of inflammatory factors and played a therapeutic role.For most chronic gastritis, HP infection is the most important reason. Toyoda et al. [14] infected 6-week-old male Mongolian gerbils with HP and then fed a diet containing CAP. It was

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found that the infiltration of inflammatory cells in the gastric mucosa was significantly inhibited at 13 weeks, and CAP was found to inhibit the proliferation of HP in vitro by bacterial culture and determination of colony forming units. De Freitas et al. [15] found that CAP not only relied on its direct antibacterial activity but also had an anti-inflammatory effect by inhibiting the expression of TNF-αin the mouse inflammation model treated with CAP.This fully shows that for chronic gastritis caused by HP infection, CAP can not only inhibit the expression of inflammatory factors, relieve existing symptoms, but also inhibit the proliferation of HP, remove the cause, and play a dual role.

4. CAP and gastric ulcer

Gastric ulcer (GU) is a chronic ulcer located between the cardia and pylorus. Its formation and development are related to the digestion of gastric acid and pepsin. About 40 % of the population in developed countries suffer from the disease, and about 80 % in developing countries. About 4 million people in the world are affected by this every year, so it is a frequent and common disease [16].

GU is a multifactorial disease with complex etiology. It is currently recognized that the main pathogenic factor is HP infection that damages the gastric mucosa, causing gastric acid to destroy gastric tissue and lead to GU. Clinically, the conventional treatment of GU is nothing more than reducing the damage factors, inhibiting acid and protecting the stomach. However, CAP almost meets all the above effects. For GU caused by HP infection, taking appropriate amount of CAP can not only inhibit the reproduction of HP, but also reduce the level of inflammatory factors, thus alleviating the existing symptoms. For another pathogenic factor, CAP can reduce gastric juice production and improve gastric secretion response. Maramag et al [17] used CAP to treat severe GU, and found that the use of CAP reduced the amount of gastric juice production, shortened the cycle of GU, and improved the histological changes caused by ulcers. At the same time, CAP itself can improve the gastric mucosal potential difference and help protect the gastric mucosa. In addition to excessive gastric acid secretion, reduced gastric mucosal blood flow is also an important cause of ulcers. Mózsik Gyula [10] found that CAP can stimulate CGRP released by TRPV1 receptor, promote vasodilation, increase blood flow, inhibit gastric acid secretion and prevent the occurrence and development of GU, which is particularly applicable to stress ulcer caused by shock, trauma, surgery, etc. Therefore, for high-risk groups with stress ulcer, the benefits of prophylactic use of CAP are self-evident.Although a large number of studies have found that moderate intake of CAP will not aggravate the development of GU, on the contrary, it will have a positive effect on its treatment, but excessive intake of CAP will also aggravate gastric mucosal injury. Larauche[18] used different doses of CAP to intragastrically administer GU mice, and determined the defunctionalization of afferent neurons by evaluating the wiping movement when the mice were perfused with 0.1 % ammonia solution. It was found that local application of low-dose CAP to stimulate sensory nerves can reduce gastric mucosal lesions caused by ulcers, and the application of neurotoxic doses of CAP will lead to desensitization or destruction of sensory afferent nerves, showing a long-term loss of reactivity to CAP itself or other stimuli of sensory neurons, aggravating the damage of stimulating factors to acute gastric mucosa. Horie[19] studied the pharmacological effects of CAP on GU in gastric antrum ulcer model rats. The results showed that a small amount of CAP could inhibit the formation of gastric antrum ulcer and promote ulcer healing, while the dose of neurotoxic CAP could make gastric antrum ulcer worse. Therefore, in the process of using CAP to prevent or treat GU, the correct dose is particularly important. Finding the most appropriate dose of CAP is also an urgent problem we need to solve.

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5. CAP and gastric cancer

Gastric cancer is the fifth most common tumor in the world and one of the most common malignant tumors in China. Its incidence ranks first among all kinds of tumors. About 170,000 people die of gastric cancer every year. Gastric cancer is harmful. Relevant studies suggest that its etiology is related to eating habits and gastric diseases. Gastric cancer occurs in people over 50 years old, and its early clinical symptoms are often not obvious and easy to be ignored. When the symptoms are obvious, they often reach the middle and late stages[20,21].

A U.S. study [22] reported that among a sample of more than 560,000 adults aged 18 years in four countries, people who eat spicy foods regularly had a 23 % lower risk of gastric cancer death than those who don 't. A large number of studies have shown that low doses of CAP can inhibit the development of various forms of human cancer. CAP can effectively inhibit tumor growth and induce apoptosis, and has no toxic effect [23]. Hai-Ning YU[24] studied the effect of CAP on gastric cancer cells and normal epithelial cells. The results showed that CAP could induce apoptosis of GES-1 cells (immortalized gastric mucosal epithelial cells) and gastric cancer cells SGC-7901 cells. MTT assay showed that SGC-7901 cells were more susceptible to CAP and its analogues than GES-1 cells. These data indicate that CAP can induce apoptosis of cancer cells. In addition to inducing apoptosis, CAP can also inhibit the invasion of gastric cancer cells in a dose-dependent manner. Gang Jia[25] characterized CAP as a lysine-specific demethylase 1A (KDM1A/LSD1) inhibitor in the experiment, which can directly and reversibly bind to KDM1A recombinants. Further cell studies have confirmed that capsaicin can bind and inhibit KDM1A in gastric cancer cell line BGC-823, and further inhibit cell invasion and migration by reversing epithelial-mesenchymal transition. Other studies have shown that the transition from carcinoma in situ to invasive cancer must be accompanied by the formation of new blood vessels. Therefore, inhibiting angiogenesis is a very effective strategy for the treatment of gastric cancer and preventing its metastasis [26].Angiogenesis refers to the growth of new blood vessels from the original blood vessels, which is a complex multi-step process, including endothelial cell activation, cell proliferation, invasion, chemotaxis, migration and differentiation into new blood vessels [27]. Appropriate amount of CAP has the potential to inhibit angiogenesis. Min Jeong-Ki[28] studied the effect of CAP on vascular endothelial growth factor (VEGF) -induced angiogenesis in vitro, and found that appropriate amount of CAP significantly inhibited primary culture-induced proliferation, DNA synthesis and capillary-like tube formation. In vivo, CAP inhibited VEGF-induced angiogenesis in rat aortic ring experiments and VEGF-induced angiogenesis in mouse matrix plug experiments. In many experiments, CAP can effectively inhibit the proliferation and invasion of vascular endothelial cells induced by VEGF, showing that CAP has significant anti-angiogenic potential and prevents the deterioration of gastric cancer to some extent. It is not difficult to conclude that CAP can directly promote the apoptosis of gastric cancer cells, inhibit the invasion of gastric cancer cells, the malignant transformation of gastric cancer, and even improve the chemotherapy resistance of gastric cancer. For the treatment of gastric cancer, chemotherapy is a necessary means, 5-FU is commonly used in the treatment of gastric cancer chemotherapy drugs. However, one of the main complications of 5-FU in clinical application for more than 50 years is chemotherapy resistance, which is the key to overcome in cancer treatment. Meral[29] used CAP to act on HGC-27 gastric cancer cells and found that the viability of HGC-27 gastric cancer cells decreased significantly. In addition, when CAP was combined with l5-FU, the inhibition of HGC-27 gastric cancer cell viability was significantly higher than that of 5-FU alone. These results indicate that CAP has a significant anti-cancer effect whether it is used alone or in combination, especially when it is used in combination, the inhibition of gastric cancer cell proliferation is enhanced, and chemotherapy resistance is effectively improved.Therefore, CAP also plays a vital role in the early prevention and treatment of gastric cancer.

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Some scholars also suspect that CAP is a carcinogen, co-carcinogen or tumor promoter, but it requires ultra-high doses and long-term exposure to high concentrations of CAP. Deng [30] used gastric cancer cell MKN-45 to establish a mouse gastric orthotopic tumor model, and gave CAP (50mg/kg, 100mg/kg) diet intake. Only in the high dose (100mg/kg) group, CAP activated TRPV1 on gastric cancer cells and promoted its expression, which in turn affected the polymerization of cytoskeletal proteins, regulated the deformability of gastric cancer cells, and promoted gastric cancer invasion. Another result showed that CAP did not change the proliferation of gastric cancer cells within a certain concentration range, and it was verified by in vitro 3D tumor sphere experiments that CAP could promote the migration and invasion of gastric cancer cells in a concentration-dependent manner. Although CAP may also cause cancer or promote the risk of cancer, it is not necessary to worry too much. Normal people eat about 5-15 g of pepper every day. However, the content of CAP in pepper with the highest CAP content is only 0.353 mg/g, while the content of CAP in pepper eaten normally is only 0.021 mg/g, which is far less than the dose of carcinogenic effect mentioned above [31]. Therefore, for patients with gastric cancer, CAP is more of its strong tumor suppressor activity. Although excessive CAP will accelerate the invasion of gastric cancer and increase the risk of gastric cancer, it requires high doses to achieve.

6. CAP and functional dyspepsia

Functional dyspepsia (FD), also known as dyspepsia, is a common gastrointestinal disease with symptoms such as upper abdominal distension, early satiety, belching, loss of appetite, and nausea. The etiology and pathogenesis of FD are not yet clear, and the pathological mechanism is complex. At present, visceral hypersensitivity and increased acid secretion have received extensive attention [32]. A large number of studies have found that visceral hypersensitivity to mechanical and chemical stimuli is a key mechanism of FD, and TRPV1 plays an important role in visceral hypersensitivity. [33] 30 patients with FD and 30 normal controls were examined by electronic gastroscopy, and the expression of TRPV1 in gastric mucosa was detected. The results showed that the expression of TRPV1 in FD patients was significantly higher than that in the control group. Choi[34] found that the symptoms of upper abdominal discomfort in FD patients were positively correlated with the serum level of TRPV1.In the follow-up, it was found that the serum TRPV1 level of patients with improved symptoms also decreased, which indicated that TRPV1 was closely related to FD. However, CAP is an important factor in activating TRPV1, and its effect on FD is also crucial.Hammer J[35] gave 49 patients diagnosed with FD a daily dose of 0.25 mg CAP for four weeks. It was observed that in patients with long-term intake of CAP, all assessed upper abdominal symptoms were improved, and visceral sensitivity to mechanical and chemical stimulation was reduced. This may be related to the desensitization of CAP by TRPV1. Oshima[36] administered acid and water to 23 FD patients and 32 healthy subjects. The results showed that the severity of symptoms caused by acid perfusion in FD subjects was significantly greater than that of water perfusion. The severity of gastrointestinal symptoms caused by acid perfusion in FD patients was significantly greater than that in the healthy group. Although the mechanism of excessive gastric acid secretion affecting FD is not clear, proton pump inhibitors can play an effective role in the treatment of FD. Therefore, the treatment of FD from acid suppression is also a common idea, and many experiments above have also confirmed that an appropriate amount of CAP can effectively inhibit the secretion of gastric acid. Therefore, for the treatment of FD, CAP can not only reduce the visceral sensitivity to mechanical and chemical stimulation, but also play a role in inhibiting gastric acid.

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7. Summary

In summary, pepper is widely consumed as a spice in the world, and CAP is the main active ingredient of pepper. The main site of action is TRPV1, which has obvious indirect or direct anti-inflammatory, acid suppression, dilation of blood vessels, protection of gastric mucosa, anti-cancer, and reduction of visceral sensitivity. It has a significant impact on the occurrence and development of gastric diseases, so it is of great social significance to study its medicinal value. Because the effect of CAP on gastric diseases is closely related to the dose, and CAP itself has a stimulating effect, it is often accompanied by adverse reactions such as gastrointestinal spasm, stomach pain, nausea, diarrhea and vomiting during use. Therefore, there are still many problems in the clinical application of CAP as a feasible drug for gastric diseases. CAP is a hot topic in recent years. This paper discusses the research progress of the effect of CAP on the mechanism of gastric diseases, hoping to provide reference for future research on avoiding the side effects of CAP and exerting the positive effects of CAP.

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