Comparative effects of capsaicin in chronic obstructive pulmonary disease and asthma (Review)

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Abstract. Chronic obstructive pulmonary disease (COPD) and asthma are chronic respiratory diseases with high prevalence and mortality that significantly alter the quality of life in affected patients. While the cellular and molecular mechanisms engaged in the development and evolution of these two conditions are different, COPD and asthma share a wide array of symptoms and clinical signs that may impede differential diagnosis. However, the distinct signaling pathways regulating cough and airway hyperresponsiveness employ the interaction of different cells, molecules, and receptors. Transient receptor potential cation channel subfamily V member 1 (TRPV1) plays a major role in cough and airway inflammation. Consequently, its agonist, capsaicin, is of substantial interest in exploring the cellular effects and regulatory pathways that mediate these respiratory conditions. Increasingly more studies emphasize the use of capsaicin for the inhalation cough challenge, yet the involvement of TRPV1 in cough, bronchoconstriction, and the initiation of inflammation has not been entirely revealed. This review outlines a comparative perspective on the effects of capsaicin and its receptor in the pathophysiology of COPD and asthma, underlying the complex entanglement of molecular signals that bridge the alteration of cellular function with the multitude of clinical effects.

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Contents

1. Introduction

Chronic obstructive pulmonary disease (COPD) and asthma are two common respiratory diseases with distinct pathophysiology that share some clinical features such as cough, shortness of breath, and wheezing, making differential diagnosis an essential step in their management (1-3). Despite great progress in understanding the molecular mechanisms governing the development and evolution of these conditions,

there is still room for improvement in setting an early diagnosis and providing effective therapy.

COPD is one of the most common causes of death, an important chronic morbidity, and is characterized by persistent respiratory symptoms and airflow limitation due to anomalies of the airways and/or alveolae caused by exposure to toxic particles or gases (1). Asthma is a treatable and common disease that causes symptoms such as shortness of breath, chest tightness, and wheezing (2). Even though the two diseases are characterized by an obstructive syndrome, there are many differences between the two entities, the most representative consisting of the fact that COPD has less variability and is never completely cured, while asthma shows reversibility. Some patients may be affected by both diseases simultaneously (3). The comparative pathogenesis of COPD and asthma is shown in Fig. 1.

Capsaicin, the most pungent substance in chilli peppers, is an intensely studied molecule, with many applications in various diseases due to its anti-inflammatory and antitumoral properties (4-7). In the pulmonary system, capsaicin is used as an index of bronchial hypersensitivity, being able to produce cough and sustained bronchoconstriction, in a dose-dependent manner when inhaled (8-10). Transient receptor potential cation channel subfamily V member 1 (TRPV1) is the receptor for capsaicin in the human body. Capsaicin cough challenge shows a good correlation with the presence or absence of pathological cough (11). Capsaicin is used in many studies as a chemical agent in the diagnosis or treatment of various disorders, including respiratory conditions (12-15). A better understanding of the effects of capsaicin in COPD and asthma may reveal new ways to diagnose and differentiate these diseases and potentially new directions of treatment.

2. Capsaicin and its receptor in the pulmonary system

Intensely studied in various conditions and on different experimental models, in the respiratory system, capsaicin has demonstrated great pleomorphism in its actions and is closely involved in triggering an abundance of signaling pathways, at times showing converse effects in pathological situations (16). Prolonged exposure to capsaicin aerosols such as those dispersed for crowd control may be toxic, irritating the respiratory tract and causing nerve damage (17,18). In extreme doses and under certain conditions, capsaicin may cause significant respiratory symptoms such as sneezing, cough, excessive mucus secretion, pain, and severe complications, and was demonstrated to be lethal in certain concentrations on test animals (18,19). Moreover, in murine models, it was shown that the intravenous administration of capsaicin instantly induces apnea, followed by an increase in the respiratory rate (20). These acute effects could be reduced by vagotomy, but not in all situations (20,21). However, in a clinical setting, when studying the beneficial effects of capsaicin in respiratory conditions, the doses of inhaled capsaicin are far too low to trigger significant adverse effects (22-24).

While capable of inducing direct effects, most of capsaicin's actions are mediated through its receptor, TRPV1. TRPV1 is a non-selective receptor that structurally belongs to the TRP family of ion channels. Besides capsaicin, it may be activated by different factors such as high temperature, acidity (pH <6.0), endocannabinoids, endogenous lipids, and other potential activators, such as numerous mediators of inflammation or various neurotransmitters (25,26). The receptor activation sends impulses to the spinal cord and brain producing a variety of effects, such as sensations of burning, stinging, itching, warming, or tingling. The terminations of the capsaicin-sensitive nerves include numerous neuropeptides, for example, substance P (SP) or calcitonin gene-related peptide (CGRP). Their activation is followed by a temporary inflammatory process known as neurogenic inflammation because of the local release of pro-inflammatory peptides (27-30). Even though the number of TRPV1 receptors in the respiratory tract is not as high as in the other regions of the body (31), they can be found in all organs and structures of the respiratory system (32). Various pathogenic processes may influence the distribution of receptors, as was revealed in patients with emphysema which show higher levels of TRPV1 receptors in the respiratory system compared with healthy subjects (33,34). TRPV1 receptors are mainly expressed in lung C-fiber afferents (35) generally recognized as fibers with polymodal sensitivity, which originate from nociceptive neurons (36). Most C-fibers are receptive to capsaicin, which acts as an important respiratory irritant (37). TRPV1 was also identified in bronchial epithelial cells (28). Alongside TRPV1, the Transient Receptor Potential Ankyrin 1 (TRPA1) receptor was revealed as being co-expressed in the airways in a population of C-fibers, and it was shown to be permeable to calcium ions (38). Although not directly stimulated by capsaicin, TRPA1 may be activated by various natural products (39), but also may be sensitized through inflammatory signaling pathways that also involve TRPV1, potentially contributing to increased chemical sensitivity (38,40,41).

TRPV1 may be activated by various ligands, including derivates of ployunsaturated fatty acids, oxytocin, neurotransmitters, chalcone derivatives, and cannabinoids (42-46). Cannabinoids are of particular interest, as they have demonstrated some similarities to capsaicin in regard to their anti-inflammatory and anti-tumoral effects in various organs, albeit some of these are mediated by specific receptors (47). Cannabinoids are not able to induce similar channel states as capsaicin on TRPV1 but they manage to target the receptor and can interact with other receptors from the TRP family, as well, which emphasises the potential interaction and synergic effects of these substances (48). Cannabinoids exert a series of TRPV1 effects and the modulation of the endocannabinoid system has proven extremely important in managing a variety of disorders affecting the central nervous system as well as conditions with intestinal, pulmonary, and cutaneous locations, a virtual structure termed 'gut-lung-skin axis' (49-52).

The activation of TRPV1 has demonstrated a variety of effects (53). Several studies have shown that TRPV1 agonists may cause apoptosis of human lung cells in alveolar epithelial cells (54,55). The inhalation of capsaicinoids for 30 min in rats causes an inflammatory reaction of the airways, destruction of epithelial cells of the trachea and nasal cavity, and injury to the bronchiolar and alveolar cells (54). Furthermore, an *in vivo* murine study has shown that a TRPV1 antagonism reduces the destruction of epithelial cells, preventing apoptosis (56). One of the frequently studied

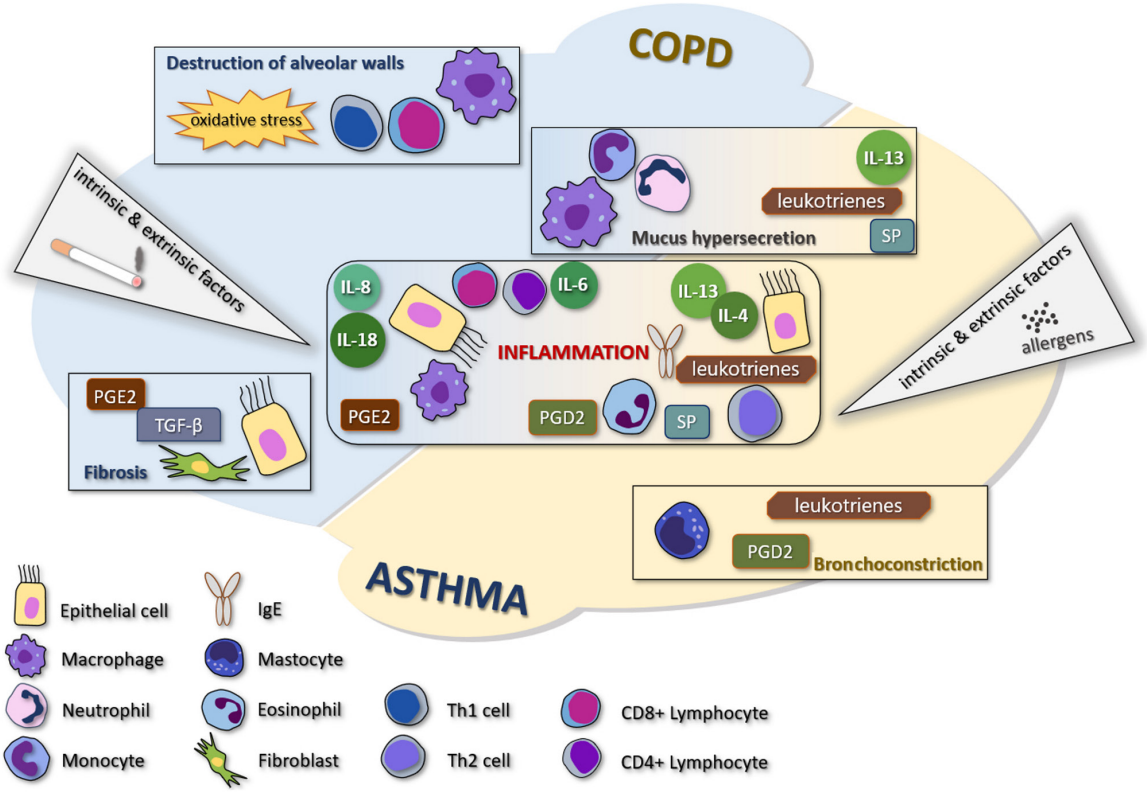

Figure 1. Comparative presentation of the most common cellular mechanisms involved in the development of the major symptoms and clinical elements of COPD and asthma. COPD, chronic obstructive pulmonary disease; TNF, tumor necrosis factor; PG, prostaglandin; SP, substance P; IL-13, interleukin-13.

TRPV1 antagonists is capsazepine. Capsazepine is a specific antagonist of capsaicin-induced C-fiber activation and has been used to uncover additional roles of the TRPV1 receptor, specifically, its involvement in the onset of clinical respiratory symptoms (57-59).

TRPV1 may mediate cough (60) and bronchoconstriction, and the use of capsazepine reduces these symptoms *in vivo* (61). Furthermore, two additional TRPV1 antagonists demonstrated similar effects in inhibiting acid-induced cough in guinea pigs. These antagonists have similar effects and efficacy to that of codeine (62).

Within the respiratory system, identical signaling pathways regulate the onset of cough, bronchoconstriction, and airway narrowing, while also enhancing the sensation of irritation as well as fluid secretion. Stimulation of airway neurons may have favorable or unfavorable effects. It was reported that it might contribute to airway protection, disposing of chemical irritants and pathogens that cause infections, while preserving and initiating tissue recovery and favoring the immune responses in murine models (63,64). However, the stimulation of airway neurons may cause inflammation in the respiratory airways that complicates underlying diseases, as was demonstrated on TRPV1 neurons in mouse models of asthma (65). A recent study by Baral *et al* indicates that pulmonary TRPV1 neurons are involved in cross-talk with immune cells via CGRP, SP, glutamate, and other signaling molecules, showing that these neurons may cause neutrophil depletion as well as cytokine and T-cell release impairment (66). These converse findings reinforce the need to further study the cascade of intricate effects triggered by TRPV1 activation and to develop novel models capable of properly translating the *in vivo* actions of capsaicin. In some respiratory diseases, a variety of pro-inflammatory mediators and peptides are involved, such as histamine, prostaglandins, cysteinyl leukotrienes, proteases, growth factors, and bradykinin (64,67). Bradykinin is a pro-inflammatory molecule, acting through B1 and B2 receptors found in the respiratory system, which can also be involved in neuroinflammation associated with an increase in SP and CGRP (64). Bradykinin causes cough and bronchoconstriction (67,68) and is involved in airway chronic inflammation, responsiveness, and remodeling through activation of a variety of cells that cause these unfavorable effects (69).

Capsaicin and the major clinical respiratory symptoms. Inhaled capsaicin is the main agent for the measurement of cough reflex sensitivity because of a lack of side effects when properly administered, low price, and good correlation with the presence or absence of pathological cough. A review from 2005 that contained 122 published studies (1984-2005) on 4.833 subjects, including healthy subjects, patients with COPD, asthma, and other diagnoses, did not manage to isolate a single serious adverse effect of inhaled capsaicin in controlled conditions when using regulated concentrations (11). The usual symptoms reported during capsaicin cough challenge are increased cough, rhinorrhea, and throat and eye irritation (70).

Asthmatics without cough could not be differentiated from healthy individuals after the capsaicin cough challenge. Moreover, it was demonstrated that hyperresponsiveness of airways and cough were mediated through different neural pathways (71).

In vitro research using fiberoptic bronchoscopy in order to obtain mucosal biopsies from 29 patients with chronic cough showed an increase in the number of TRPV1 receptors in these subjects compared to 16 controls. Those data demonstrate a correlation between chronic cough and TRPV1 receptors. The cause of the increase was not determined. The subjects also received aerosols of a capsaicin solution dissolved in 0.9% sodium chloride until cough was produced five or more times. Results suggest an increased frequency of cough when capsaicin was inhaled by patients with chronic cough (72). In addition, cold air seems to increase the sensitivity of TRPV1 to capsaicin and increase cough sensitivity (73).

In an *in vivo* study on guinea pigs, the delivery of capsaicin by aerosol to the airways induced cough, while the administration of a capsaicin antagonist caused a decrease in the induced cough (74). The antagonist for capsaicin used in that study completely blocked the receptor for capsaicin and prevented its response to the variation of pH. Additionally, it inhibited the influx of Ca^{2+} that blocks the effects of capsaicin. This is paramount evidence of the major role of capsaicin in cough and is an important finding for basing future human trials. In terms of the action mechanism, it appears that the effects of capsaicin were carried on by direct TRPV1 effects but also mediated by tachykinins such as SP and neurokinin A (NKA) (74).

Long-term respiratory effects after exposure to capsaicin aerosols were analyzed in several major studies. Two studies showed no difference between hot pepper workers and healthy individuals in regard to their pulmonary function (75,76).

In vitro and *in vivo* studies suggested that capsaicin can be mutagenic; conversely, multiple studies revealed that topical, dietary, or injected capsaicin may demonstrate a chemoprotective effect (77-80).

Two decades of experience with capsaicin demonstrated that the capsaicin cough challenge is a safe investigation, and this procedure may prove to be an extremely important tool for future research.

The effects of capsaicin on mucus secretion in COPD and asthma were also investigated. *In vitro*, findings of several studies showed that SP stimulates mucus secretion in the respiratory system (81-83) and an increase of SP appears after stimulation of sensory nerves by capsaicin (84). In an *in vivo* study by Karmouty-Quintana *et al* increased mucus production caused by the activation of airway sensory nerves with intratracheal administered capsaicin was observed, and the results were confirmed showing a reduced level of mucin concentration after administration of capsazepine, a TRPV-1 antagonist. These effects seem to be mostly determined by SP, CGRP, and NKA released as a response to sensory nerve stimulation by capsaicin (85).

Dyspnea is a common respiratory symptom in both COPD and asthma, however, it has different attributes. In COPD, dyspnea is progressive and proportional to the airflow obstruction, while in asthma it appears simultaneously with the transitory bronchoconstriction (86). Dyspnea is a symptom that appears after the stimulation of adenosine receptors, and capsaicin shows no interference with these receptors (87). When investigated in clinical applications, no evidence that capsaicin may cause dyspnea was found, neither inhaled nor administered intravenously, in tolerable doses (88,89).

Smoking is a major causative and aggravating factor in lung inflammation. However, acute and chronic infection, whether viral, bacterial, or fungal, may influence the prognosis of these patients and their response to treatment (90). Some of the infections trigger exacerbations and cause a decline in lung function, while the patient does not benefit from effective therapeutical strategies, which poses significant problems in the management of these patients (91). The lung microbiome may experience changes related to the exacerbations and may influence biomarkers such as sputum neutrophils percentage and IL-8, as well as serum IL-10 and MMP-7 (92). Capsaicin has demonstrated antimicrobial properties and may provide an added benefit in COPD patients with concurring infections, a research direction which needs to be further explored (93).

3. Capsaicin in chronic obstructive pulmonary disease

COPD is one of the leading causes of death and an important chronic morbidity featuring limitation of airflow, cough, mucus hypersecretion, and dyspnea. It is caused by long-term exposure to toxic particles or gases, usually tobacco smoke, and may sometimes affect patients with various genetic abnormalities or concurring respiratory diseases (94). COPD demonstrates a steady increase in mortality and morbidity and is estimated to maintain this trend (95). Besides the clinical context, spirometry is necessary for the diagnosis by confirming the airflow limitation that is established when forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) ratio is under 70% of the normal limits after the use of a bronchodilator (96). In their clinical evolution, patients with COPD can have periods of time when they show no symptoms, and periods of exacerbations (1).

Capsaicin, smoking and inflammation in COPD. Inflammation is one of the fundamental characteristics of COPD. It accelerates the disease progression and it is not reversible. Inflammation in COPD is usually a consequence of smoking, which is a major factor in the pathogenesis of COPD. Most cigarette smokers have a chronic cough, which is usually present prior to the onset of airflow obstruction. Smoking induces airway inflammation causing an increase in the number of neutrophils, macrophages, and T lymphocytes ($CD8^+$ and $CD4^+$) (97). These cells release a large number of cytokines and mediators that initiate and maintain the inflammatory process (98). The mediators with increased concentrations in COPD are leukotriene B4, neutrophil and T-cell chemoattractant, chemotactic factors such as interleukin (IL)-8 and growth-related oncogene α, pro-inflammatory cytokine (TNF)-α, IL-1β, IL-6), and transforming growth factor-β (98,99). Alongside the inflammatory process, an imbalance between protease and antiprotease activity can be identified in COPD. This results from the intensified production and activity of proteases and decreased production and activity of antiprotease, caused by cigarette smoke and inflammation. Neutrophils release elastase, cathepsin G, and protease 3, while macrophages produce cysteine protease, cathepsins E, A, L, S, and matrix metalloproteinase-8, -9 and -12. α1 antitrypsin, secretory leucoprotease inhibitor, and tissue inhibitors of metalloproteases are the major antiproteases that participate in emphysema in COPD (31,98,100). The alteration

of parasympathetic afferent and efferent fibers may contribute to the onset of bronchospasm, cough, and dyspnea (101).

In vivo, in a study on mice after exposure to cigarette smoke, the levels of leukocyte infiltration and the high level of inflammatory mediators caused the progression of COPD and the decline of lung function. These processes increased the production of IL-1β and IL-18, two cytokines released in association with the stimulating action of TRPV1 agonists, including capsaicin, in a cell-based model using primary human cells (33). Moreover, TRPV1 is found in $CD4^-$ T cells in mice. These receptors are activated after stimulation of the T-cell antigen receptor, which contributes to the influx of Ca^{2+}. After this influx, the T cells are activated playing an important role in the development of inflammation. This process indicates that TRPV1 may have a fundamental function in the inflammatory process, particularly after smoke exposure, which is the main cause of COPD (102).

Recent studies also revealed the role of TRPV1 in mediating the effects of cigarette smoke on the alveolar epithelial cells through the increase of inflammation, oxidative stress, and mitochondrial damage (103,104). In patients with COPD, TRPV1 mRNA expression is increased in comparison with non-smokers (33).

The expression of TRPV1 is related to the intensity of the inflammatory process induced by cigarette smoking (105). In a mouse model, Jian *et al* have shown that the decreased expression of TRPV1 by using total flavonoids is followed by a subsequent decrease in the inflammation and oxidative stress in the lung parenchyma (106). A 2020 article has shown that single nucleotide polymorphisms of TRPV1 are associated with a higher risk of developing COPD in smokers (107).

In another study, human cells were exposed to cigarette smoking, and the expression of TRPV1 in pulmonary tissue was increased, as was the concentration of pro-inflammatory cytokines (108).

Stimulation of TRPV1 in COPD releases inflammatory neuropeptides which increase vascular permeability, cause extravasation of plasma proteins, bronchoconstriction, and amplify the concentration of mucus (109,110). Mucus hypersecretion causes increased sputum production and seems to correlate with the severity of COPD (111).

Interestingly, *in vitro* studies showed that cigarette smoke can cause neuropeptide release by stimulating TRPA1 and acetylcholine receptors, contributing to the inflammatory process, with decreased or lack of TRPV1 involvement (112). Conversely, *in vivo* murine models suggest that the mediation of inflammation is exclusively performed by activation TRPV1 and 4, and not by TRPA1 (33). These contradictory findings require the need for future studies, ideally on human subjects.

Capsaicin stimulates TRPV1 with further release of pro-inflammatory cytokines in the airways. Activation of TRPV1 by capsaicin in patients with COPD stimulates the secretion of ILs, TNF-α, and prostaglandin E2 (PGE2) (113). Special attention was paid to the capsaicin-induced stimulation of IL-6 production in human respiratory epithelial cells (114). IL-6 has a very important role in the transition from acute to chronic inflammation because it stimulates T-cells and B-cells. This stimulation favors a chronic inflammatory response due to the activation of endothelial cells that release IL-8 and monocyte chemoattractant protein 1 and activate the expression of adhesion molecules (115). Nassini *et al* used mouse models and *in vitro* studies on human small airway epithelial cells, fibroblasts and smooth muscle cells exposed to cigarette smoke to demonstrate that capsaicin inhalation stimulates TRPV1 receptors in sensitive nerve fibers promoting neurogenic inflammation and favoring the release of IL-8, most likely through coactivation of TRPA1 receptors in non-neuronal cells (116). This mechanism may maintain and even increase inflammation in patients with COPD, enhancing its negative effects. Furthermore, bronchoconstriction may exacerbate the airflow limitation and intensify the dyspnea of patients.

Studying the *in vivo* response of the exposure of guinea pigs to cigarette smoke revealed that nebulized capsaicin enhances cough production in smoke-exposed animals, through a non-cyclo-oxygenase-mediated mechanism. The increased responsiveness to capsaicin appears to depend on sensory nerves containing CGRP-like substances (117). Moreover, while increasing sensitivity to capsaicin, exposure to smoke seems to decrease the response to PGE2, promoting the concept that sensory nerves are affected in COPD in a disease-specific manner (118).

A consensus was not yet reached regarding the overall effects of capsaicin in patients with airflow obstruction. A large cross-sectional study by Blanc *et al* (119) compared the effects of inhaled capsaicin on non-smokers and smokers with and without airflow obstruction. An increase of responsiveness in all groups of patients was demonstrated, more significantly in patients with COPD. Asymptomatic smokers registered no complaint, despite their hyperresponsiveness to capsaicin compared to non-smokers. In the same study, women were more sensitive than men in all three groups (119). However, no correlation was identified between the cough response intensity and the degree of airflow obstruction in COPD patients appreciated by FEV1 values, and these findings were confirmed in another study, by Doherty *et al* (120). Conversely, research data published in 1999 showed no significant difference in cough sensitivity to capsaicin between patients with COPD and airflow obstruction compared to healthy controls (121).

Capsaicin and cough in COPD. TRP channels have a protective role in physiological situations when the airways are not affected by pathological changes. In a disorder such as COPD, this role can be altered, and TRP channels may be responsible for the symptoms of COPD, especially cough and they may also participate in the inflammatory process identified in COPD (32).

Cough is usually the first symptom in patients with COPD. Cough may be sporadic and sometimes unproductive (1), it can affect the quality of life in patients with COPD and this is an important reason to research it and potentially identify new therapies (122). C and Aδ fibers are expressed in the mechanism of pathological cough, so TRP ion channels are an important component of this process (38). Capsaicin is the most common and usable agonist of TRPV1, used in a variety of studies on patients with chronic cough, a category that includes patients suffering from COPD (123,124).

Several clinical studies using capsaicin aerosols have been developed for patients with cough and COPD. Capsaicin responsiveness and cough in COPD was researched in a study by Doherty *et al* (120). The presented data suggest that inhaled

capsaicin caused an increase in cough in patients with COPD and no relationship between cough and airflow limitation after exposure to capsaicin was observed (120). Another study, by Terada *et al* (125), showed an increase in the number and frequency of exacerbations after capsaicin inhalation in patients with COPD compared to controls, demonstrated by lower concentrations of capsaicin needed to produce five or more coughs; furthermore, bronchial hypersensitivity correlated with the frequency of exacerbations and the serum C-reactive protein, indicating that ongoing airway inflammation is associated with hypersensitivity of the cough reflex to capsaicin and may precipitate the exacerbations (125). Capsaicin cough challenge may be an important aid in assessing, managing COPD and its complications, and advancing the development of a new antitussive therapy. It does not yield serious adverse effects as it was demonstrated in a paper reviewing 20 years of practicing capsaicin cough challenge (11). A cough challenge test performed on 20 patients with exacerbated COPD revealed that their sensitivity to capsaicin was increased compared to the repeated test after recovery, and if hypersensitivity was maintained during recovery this announced future exacerbations (126).

4. Capsaicin in asthma

Asthma is a chronic, frequent, and treatable pulmonary disease characterized by respiratory symptoms, limitation of activity, and exacerbations that occasionally need urgent medical care, and can be a potentially lethal condition. The most common respiratory symptoms in asthma are wheezing, shortness of breath, cough, chest tightness, and variable expiratory airflow. The main risk factors that may aggravate asthma are viral infections, allergens, tobacco smoke, pollens, food, drugs, or exercise. Spirometry is required to set the diagnosis: FEV1 increases by 12% and a minimum of 200 ml of the baseline values post-bronchodilator (2).

Asthma is regarded as a typical Th2 disease, with increased immunoglobulin E (IgE) levels, airway inflammation, and the presence of numerous eosinophils. Usually, patients begin suffering from asthma in childhood. The allergens are inhaled and stimulate Th2-helper cell proliferation and the increase of IL-4, IL-5, and IL-13 levels (127). A fundamental characteristic of these patients is long-term airway inflammation. Consequently, chronicity and disease evolution disease may occur. The roles of IL-4 are to support B-cell isotype swapping, increase the response of stimulus of adhesion molecules, eotaxin creation, and improvement of airway hyperresponsiveness and goblet cell metaplasia (128-130). IL-13 partly shares its receptor with IL-4 and plays a critical role in the pathophysiology of asthma by increasing mucus secretion and modulating the functions of epithelial cells (131). Eosinophils and IgE are also of great importance in asthma and act via distinctive pathways which do not interfere with the mechanisms of IL-13 (132,133).

TRPV1 and allergens in asthma. TRPV1 may play important roles in the modulation of the pathogenic changes occurring in asthma (105). The expression of TRPV1 and Th2 levels seems to correlate with the asthmatic debut in the pediatric population (134). Recent data showed that TRPV1 can mediate the response of epithelial cells to allergens, increasing IL-33 secretion and the activation of dual oxidase 1 and epidermal growth factor receptor (135). Furthermore, an *in vivo* study on mice published in 2020 has shown that TRPV1 stimulates the production of mucus and cytokines in asthma by regulating the expression of MUC5AC and nuclear factor kappa-light-chain-enhancer of activated B-cell pathway, with probable involvement of neuropeptides SP and CGRP (136). TRPV1 also mediates the appearance of cough via a neuronal mechanism and shows increased expression after exposure to allergens (137,138). Although expressed on airway smooth muscle cells, TRPV1 activation does not significantly contribute to the initiation of bronchoconstriction (139). *In vitro* studies have shown that coal fly ash causes TRPV1 activation and worsens asthma symptom control (140). A study on ovalbumin (OVA)-induced asthmatic mice showed that exposure to nanoparticles causes neuroinflammation mediated through TRPV1 and TRPV4, and is accompanied by an increase in SP, CGRP, and bradykinin (64). A similar study showed that a pollutant known as trimellitic anhydride can increase TRPV1 expression as well as amplify the levels of IL-13, SP, prostaglandin D2, and nerve growth factor in the lungs of OVA asthmatic mice (141). In the same experimental model, Li *et al* identified ozone as an environmental pollutant with similar effects on TRPV1 and the inflammation pattern in asthma as the allergens mentioned above (142). Small particulate matter can also inflict bronchial mucosal damage and thickening of bronchial smooth muscles in asthmatic mice (143). Combining pollutants builds a model closer to real-life situations (144), and, by doing so on allergic Balb/c mice, activation of TRPV1 signaling and increases of CGRP and SP levels were observed contributing to the neurogenic inflammation of asthma (145). Allergen exposure may lead to pathological changes outside the respiratory tract. In an *in vivo* study, Spaziano *et al* (146) showed that sensitization of the nucleus solitary tract (NST) occurs following exposure to allergens, and this is a basis for increased airway sensitivity. When capsaicin was inhaled, an increase in the neural firings of the NST were identified. However, TRPV1 may play a complex role in modulating excitation as its activation by endocannabinoids may stimulate glutamatergic signaling and alter the bronchoconstrictive reflex (146).

These observations were demonstrated by studies on the same animal model showing that inhibition of the TRPV1 mRNA and protein expression using various antagonists including capsazepine caused an improvement in pulmonary function, decreased airway hyperresponsiveness, and reduced cytokine concentrations in aggravated asthma (145,147-149). In addition, the use of allergens to induce bronchoconstriction seems to increase the TRPV1 response to capsaicin, increasing cough reflex sensitivity, as demonstrated in a recent clinical trial (150). The effects of stimulating TRPV1 receptors with capsaicin are increased in mice with atopic dermatitis to the extent that asthmatic-like inflammation of the airways is produced while compliance of the lungs is decreased (151).

In an *in vitro* study, by McGarvey *et al*, the TRPV1 protein was found in a culture with primary bronchial epithelial cells through patch-clamp experiments. That study confirmed that capsaicin induces the release of IL-8 especially in patients with chronic airway inflammation (152).

Capsaicin and inflammation in asthma. In asthma, chronic inflammation is one of the fundamental features of the disease. Inflammation progresses when inflammatory cells interact with local cells to create a cascade of events that triggers and maintains chronic inflammation and causes clinical symptoms. The consequences of inflammation in asthma are bronchospasm, airways mucus secretion and edema, bronchoconstriction, and bronchial epithelial damage (153).

The role of capsaicin in the process of inflammation in asthma is unclear, as some studies cite pro-inflammatory properties of capsaicin, while other recent studies revealed its anti-inflammatory effects (154).

However, TRPV1 activation seems to play an important role in the inflammatory cascade of asthma, and pharmacological inhibition of TRPV1 leads to a reduction in IgE levels as well as an attenuation of airway inflammation in mice (155).

In vitro, after using a TRPV1 antagonist, inflammation in the airway tissues of patients with chronic asthma was attenuated. These results may suggest that blocking TRPV1 may be a new direction for the anti-inflammatory treatment in asthma (156).

A study by Rehman *et al* showed *in vivo* that blocking TRPV1 in a murine model attenuates the symptomatology of asthma, probably by alleviating the inflammation of the airways. TRPV1 inhibition reduced the concentration of IL-13 and its effects on inflammation in the airways. Consequently, hyperresponsiveness and inflammation were reduced (157). Conversely, a different murine study revealed that inhibition of the TRPV1 gene may increase airway inflammation. The levels of the IgE, eosinophils, and IL-4 may be increased in the bronchoalveolar lavage fluid in this case. The authors revealed that the effects achieved by TRPV1 employ multiple mechanisms, both direct and mediated by SP, CGRP, NkA, and somatostatin (158).

Capsaicin and cough in asthma. Cough is a frequent and important symptom that influences the quality of life in patients with asthma (159) and is regulated by sensory nerves in the airways (60,160). In the previously mentioned *in vitro* study by McGarvey *et al*, the expression of TRPV1 in bronchial biopsies from asthmatics refractory to corticotherapy was found to be higher than that in patients without asthma or in those with asthma that were responsive to corticoids (152). Those findings were supported by Chen *et al* by analyzing TRPV1 mRNA in the peripheral blood of asthmatics and concluding that TRPV1 expression levels are major factors for bronchial asthma in children (161). As mentioned before, cold air seems to increase the effects of capsaicin on TRPV1, but humified warm air has been shown to trigger cough and bronchoconstriction in mild asthmatic patients via increased activation of C-fibers (162). While spirometry is useful in investigating the response of the large airways to capsaicin, impulse oscillometry system has proven more sensitive in detecting peripheral airway function in asthmatics and the changes induced by capsaicin (163).

In a study performed *in vivo* on asthmatic mice with cough, the inhalation of capsaicin caused a more frequent cough and was accompanied by eosinophil infiltration detected in the bronchoalveolar lavage fluid (164). There are also data showing neutrophil infiltration in the submucosal layer in asthmatic rats after the capsaicin cough challenge, an effect of both direct TRPV1 action as well as due to the release of neuropeptides (SP and CGRP) inducing neurogenic inflammation (165). A study on guinea pigs sensitized with capsaicin showed that the rate of coughs was notably increased, and the proposed mechanism was associated with airway tract eosinophilic inflammation (166).

Previous findings showed an increase in the frequency of cough in patients with asthma after inhalation of capsaicin. This is an effect of the hyperresponsiveness that characterizes patients with asthma. The mechanism probably involves neuronal dysfunction. When capsaicin stimulates the TRPV1 receptor, inflammatory mediators are released with further increased stimulation of the nerve fibers. This process determines membrane depolarization and release of the inflammatory mediators which are in high concentration in asthmatic patients (167). This is a possible explanation of why increased sensitivity to capsaicin has been identified as a risk factor for severe forms of asthma (168).

A study from 2019 comparing asthmatics and healthy controls showed no difference in the cough threshold after inhaled capsaicin between the two groups (163). However, in patients with asthma, the frequency of cough is higher than in healthy subjects. In addition, a higher sensitivity to capsaicin was identified in women and older patients (169). In asthmatic children, there is a decreased sensitivity to capsaicin compared to controls, which seems to be mediated by neurotransmitters released from parasympathetic neurons (170). This finding is strengthened by another recent study showing that some nervous phenotypes may induce excessive coughing in asthmatic patients due to a neuronal dysfunction (137,171). Capsaicin cough challenge is more sensitive in patients with cough-variant asthma even if bronchodilators were used in these patients (120). These patients have a lower quality of life because of their frequent exposure to irritants in daily life and due to their permanent discomfort. Research data have shown a direct correlation between the quality of life and sensitivity to capsaicin, as asthmatic patients with hyperactivity to inhaled capsaicin have a significantly poorer quality of life than controls (172,173).

A study published in 2020 tested the effects of inhaled capsaicin on 385 chronic cough patients, revealing that the capsaicin cough challenge is a proper method for investigating patients with variable clinical factors in asthma (174). Additionally, the test is a safe method to employ in severe asthma (175).

However, in regard to therapeutic prognostic, cough sensitivity to capsaicin may hold an important role in predicting the response to bronchial thermoplasty when used for treating patients with severe asthma (176). Alongside the different diagnostic benefits cited in asthma, capsaicin is a molecule gaining attention and is increasingly studied in animal models and human trials.

The intended finality of these findings is to improve the management of asthmatic cough. The use of the antimuscarinic bronchodilator Tiotropium has proved effective in controlling asthmatic cough in patients unresponsive to corticosteroids and long-acting β2 agonists, and it improved capsaicin cough reflex sensitivity, leading to the conclusion that its effects are mediated through sensory nerves, rather than effective bronchoconstrictors (177).

Table I. Comparison of capsaicin effects on cough and inflammation in COPD and asthma.

Component	Effect	Study type	(Refs.)
COPD			
Cough	Increase in frequency	*In vitro* (mucosal cells)	(60)
	Increase in frequency	*In vivo* (guinea pigs)	(62)
	Increase in frequency	Trial	(104,109)
	Rise of exacerbation incidence		(109)
Inflammation	Release of IL-1α, TNF-α and PGE2	*In vitro* (human primary bronchial fibroblasts)	(97)
	Release IL-8 and pro-inflammatory cytokines	*In vitro* (primary bronchial epithelia cells)	(92,136)
	Release IL-1β and IL-18		
	Maintain inflammation	*In vivo* (mice)	(32)
Asthma			
Cough	Increase in frequency	*In vitro* (bronchial cells)	(136)
	Increase in frequency	*In vivo* (guinea pigs)	(149,150)
	Increase in frequency	Trial	(151,153)
Inflammation	Pro-inflammatory	*In vitro* (bronchial cells)	(140)
	Eosinophil infiltration	*In vivo* (guinea pigs)	(150)
	Pro- and anti-inflammatory	*In vivo* (mice)	(141,142)

COPD, chronic obstructive pulmonary disease; TNF-α, tumor necrosis factor-α; PG, prostaglandin; IL, interleukin.

In summary, capsaicin demonstrates complex effects on cough and inflammation in COPD and asthma, either through direct TRPV1 activity or mediated by released factors, and these findings were summarized in Table I.

5. Conclusions

Capsaicin may exhibit a variety of clinical and paraclinical effects in COPD and asthma. Some are similar in both diseases, while others may be significantly different or opposite. In many cited studies, the frequency and intensity of cough are increased after capsaicin inhalation in COPD, while other authors report only an increase in the frequency of cough in asthmatic patients. The effects of capsaicin on inflammation in these two diseases are different. In COPD, several studies showed that capsaicin has pro-inflammatory effects, while, in asthma, the role of capsaicin in inflammation is unclear, as various studies showed conflicting results, citing pro-inflammatory as well as anti-inflammatory effects. Most authors revealed that the hyperresponsiveness to capsaicin is higher in smokers with airflow obstruction than non-smokers and smokers without airflow obstruction. Capsaicin appears to be a safe product as we failed to identify any studies showing an increase of dyspnea in COPD or asthma after capsaicin administration, when used in tolerable doses. Capsaicin may be a very promising, cost-effective, natural, and safe tool in expediting the diagnosis of COPD and asthma in the future, with increased accuracy in selected cases, especially due to its effects on cough and inflammation.

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Availability of data and materials

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Authors' contributions

MDD, CS, and CCa conceived and designed the review. CS and CCa have developed the methodology and scientific approach. Preliminary documentation, data selection and analysis, writing and editing of the original draft were performed by MDD, ASJ, CS, IAB, GDAP, AC, DOC, RSC, CCo, MN, and CCa. Content review and editing were performed by CS, AC, and CCa. Supervision was conducted by IAB, CCo, MN, and CCa. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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