

# The Role of Pain Receptors in the Main Symptoms of Covid-19 and How Diet Can Be a Therapy

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## ABSTRACT

It is estimated that 80% of SARS-CoV-2 patients have olfactory disturbances and many also have dysgeusia or ageusia (an interruption or loss of taste, respectively) or changes in chemesthesis, the ability to perceive irritants by TRP receptors. Anosmia (loss of sense of smell) and dysgeusia been termed 'sentinel symptoms'. Anosmia and ageusia represent a real health risk and can also cause nutritional deficits'. Infection with SARS-CoV-2 in the oral cavity could cause changes in the production or quality of saliva, contributing to the symptoms of taste loss. Since the activation of TRPs by Reactive Oxygen Species (ROS) contributes to inflammation and pain, research is focusing on several biological mediators related to TRPs and oxidative radicals that could help the development of treatments for pain itself and some COVID related symptoms.

Recent studies have found that Nuclear Factor Erythroid-Related Factor 2 (NRF2) is a transcription factor that regulates cellular defence against toxic and oxidative insults. Compounds that can activate or induce NRF2 include garlic H<sub>2</sub>S polysulphides, cinnaldehyde in cinnamon, polyphenols in green tea, curcumin, a polyphenolic compound found in curcuma, piperine, an alkaloid found in black pepper, and glucoraphanin found in broccoli.

In addition, there is a substantial electrophilic interaction between NRF2, TRPA1 and TPV1 that results in their desensitisation. TRPV1 receptors enter a refractory state (commonly called desensitisation) that leads to inhibition of receptor function as repeated stimulation leads to a progressive reduction in their response. To counteract some of the effects induced by SARS-CoV-2, a rapid desensitisation of TRPs by certain foods is therefore proposed which could reduce the severity of symptoms (including cough, loss of taste and smell) and provide new therapeutic strategies.

**Keywords:** Covid-19; Anosmia; Dysgeusia; Ageusia; Taste; Smell; Transient Receptor Potential (TRP) channels; Pain; Reactive Oxygen Species (ROS); Food; Nuclear Factor Erythroid-Related Factor 2 (NRF2)

## INTRODUCTION

It is estimated that 80% of SARS-CoV-2 patients have olfactory disturbances and many also have dysgeusia or ageusia (an interruption or loss of taste, respectively) or changes in chemesthesis, the ability to perceive irritants [1-6]. Anosmia (loss of sense of smell) and dysgeusia have been reported as symptoms that seem to have a particular tendency to precede the onset of respiratory symptoms. They have therefore been termed 'sentinel symptoms'. A recent observational study including more than two million participants has revealed that loss of smell and taste

is more predictive than all other symptoms, including fatigue, fever or cough [7]. These symptoms may serve as a useful additional screening criterion, particularly for identifying patients in the early stages of infection [8].

## BUT WHAT ARE THE PHYSIOPATHOLOGICAL MECHANISMS UNDERLYING THESE CHANGES?

It should be noted that the main mechanisms proposed for acute changes induced by other viruses in the olfactory region include conductive deficits caused by loss of patency due to mucosal

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swelling and increased mucus production, changes in mucus composition, and secondary changes in olfactory signaling caused by local release of inflammatory intermediates such as cytokines [9-15].

However, the natural history of COVID-19 associated anosmia supports that SARS-CoV-2 attacks the olfactory system by mechanisms distinct from those used by more benign endemic coronaviruses and does not usually cause nasal congestion. It seems that the virus mainly attacks support cells and stem cells and not directly 'olfactory neurons', but this does not mean that the neurons cannot be affected. Olfactory neurons do not have Angiotensin-Converting Enzyme 2 (ACE2) receptors, which allow the virus to enter cells, on their surface. But the sustentacular cells, which support the olfactory neurons in an important way, are studded with them. These cells maintain the delicate salt water balance of the ions present in the mucus and allow neurons to discriminate signals and send them to the brain.

If this equilibrium is disrupted there is a shutdown of neuronal signaling and thus of the sense of smell. The sustentacular cells also provide the metabolic and physical support necessary to sustain the cilia (finger-like) at the ends of the olfactory neurons where the odour-sensing receptors are concentrated [16,17]. "If you physically interrupt those cilia, you lose the ability to discriminate odours". With regard to the alteration of taste perception, the researchers focused their attention on receptor cells.

There are two types of transmembrane receptors relevant to taste:

G-Protein-Coupled Receptors (GPCRs), which mediate sweet, umami and bitter tastes, [18,19] and ion channels, which mediate sour (H<sup>+</sup>) and salty (Na<sup>+</sup>) tastes. Researchers have observed that compared to other oral tissues, the salivary gland cells of the tongue and tonsils have the Angiotensin-Converting Enzyme 2 (ACE2) receptor (to which the virus binds) and the enzyme TMPRSS that allows the virus to fuse its membrane with that of the host cell and slip inside. Therefore it would appear that infection with SARS-CoV-2 in the oral cavity could cause changes in the production or quality of saliva, contributing to the symptoms of taste loss [20]. But within the taste buds and in the epithelial cells of the tongue and mouth, the presence of TRP receptors sensitive to various chemicals such as capsaicin, allicin, gingerol, alcohol and changes in acidity (H<sup>+</sup>) has also been detected [21,22] and they too decrease their discriminatory activity in relation to changes induced in the microenvironment by COVID19 (through an oxidative storm). Anosmia and ageusia represent a real health risk and can also cause nutritional deficits'. But the role of TRP channels in the transmission of sensory stimuli is not limited to taste. They are also involved in the transduction of painful stimuli, and both (taste and painful stimuli) are essential for survival and health.

#### WHERE IS THE TRPS LOCATED?

TRP channels (example-TRPA1, TRPM and TRPV) are found in nerve endings, dorsal root ganglia and taste buds and play an essential role in pain perception and taste perception [23,24].

They are also widely expressed in small diameter sensory fibers (C and A  $\delta$  fibers) but are also present in the central nervous system and other physiological membranes of many tissues [25,26]. TRP receptors have also been observed to play a crucial role in complex pulmonary pathophysiological events, including increased intracellular calcium levels, recruitment of proinflammatory cells, neurogenic inflammatory pathways, cough reflex, mucus clearance, and disruption of epithelial integrity, pulmonary oedema and fibrosis [27]. Activation of TRPV1 increases the release of several pro-inflammatory molecules, including substance P (sP) and cytokines such as IL-6. Respiratory pathophysiology in COVID-19 cases may show mechanisms related to TRPV1 receptor sensitization resulting in hyper inflammation of the lungs and associated complications [28].

Recent studies have observed that TRPA1 and TRPV1 receptors are co-expressed in C-fiber pulmonary vagal sensory nerves are self-regulating and are sensitive during oxidative processes to Reactive Oxygen Species (ROS) [29]; a common denominator in all conditions associated with COVID-19 appears to be a storm of cytokines associated with strong oxidative stress. In particular, when TRPA1s are activated by Reactive Oxygen Species (ROS) they can increase sensory or vagal nerve discharges to evoke pain and several symptoms of COVID-19 including cough, vomiting and diarrhea [30,31]. Since the activation of TRPs by Reactive Oxygen Species (ROS) contributes to inflammation and pain, research is focusing on several biological mediators related to TRPs and oxidative radicals that could help the development of treatments for pain itself and some COVID-related symptoms. Recent studies have found that Nuclear Factor Erythroid-Related Factor 2 (NRF2) is a transcription factor that regulates cellular defence against toxic and oxidative insults through the expression of genes involved in the oxidative stress response in inflammatory processes and makes cells resistant to chemical carcinogens [32].

#### BUT WHICH COMPOUNDS HAVE THIS PROPERTY?

Many foods have antioxidant properties and several mechanisms are involved. Compounds that can activate or induce NRF2 include garlic H<sub>2</sub>S polysulphides, cinnaldehyde in cinnamon, polyphenols in green tea, curcumin, a polyphenolic compound found in curcuma, piperine, an alkaloid found in black pepper, and glucoraphanin found in broccoli [33-35]. In addition, there is a substantial electrophilic interaction between NRF2 and TRPA1 and TPV1 that results in their desensitisation. TRPV1 receptors enter a refractory state (commonly called desensitisation) that leads to inhibition of receptor function as repeated stimulation leads to a progressive reduction in their response. To counteract some of the effects induced by SARS-CoV-2, a rapid desensitisation of TRPs by certain foods is therefore proposed which could reduce the severity of symptoms (including cough, loss of taste and smell) and provide new therapeutic strategies. Glucoraphanin has been tested [33] in several clinical trials of COVID 19 with repeated dosing (every 6-8 hours) and a reduction in symptom severity was observed.

## CONCLUSION

However, the efficacy and safety of these preliminary data will need to be confirmed by further studies, which will allow us to identify the bioavailability of the active ingredients in a wide range of foods effective in reducing COVID-19 symptoms. We therefore believe that this promising research will be of great importance in providing new therapeutic strategies that will be very effective forms of defence against viral infections.

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