

Rapid TRP (transient receptor potential) desensitization in COVID-19: fact or fancy?

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Abstract

A common denominator in all conditions associated with COVID-19 appears to be the oxidative stress storm. Antioxidant nutrients may be of importance in COVID-19 through Nrf2 activation. TRP (Transient Receptor Potential) desensitization has been suggested in 6 COVID-19 patients since broccoli capsules (potent Nrf2 and weak TRPA1 agonist) reduced cough and nasal obstruction within 10-20 minutes. A series of cough induced challenges were carried out in one COVID-19 patient. Curcuma and black pepper, ginger or green tea all improved cough and nasal obstruction in less than 2 minutes. These effects were attributed to TRPA1 (Transient Receptor Potential ankyrin 1) desensitization. In the same patient, low-dose capsaicin capsules induced the same effect suggesting a TRPV1 (Transient Receptor Potential vanillin 1) desensitization. These results cannot be taken as formal evidence. However, they have contributed to developing a proof-of-concept for the hypothesis that combined Nrf2-TRPA1-TRPV1 foods may be beneficial for some COVID-19 symptoms and that there is a synergy between Nrf2 and TRPA1. Before any conclusion can be drawn and Nrf2-TRPA1-TRPV1 foods recommended for COVID-19, these data warrant confirmation using well-designed studies.

Key words: COVID-19, Nrf2, TRPA1, TRPV1, capsaicin, oxidative stress, kimchi, desensitization

Introduction

For several months, we have been proposing that differences in diet could be one among the many factors explaining the geographic differences between countries in COVID-19 death rates¹⁻³. Surprisingly, the countries that had very low death rates in the Spring pandemic are not experiencing an increase in SARS-CoV-2 infected patients in this second outbreak. The countries concerned are particularly those of Eastern Asia where fermented vegetables and spices are largely consumed.

A common denominator in all conditions associated with COVID-19 appears to be the impaired redox homeostasis responsible for reactive oxygen species (ROS) accumulation⁴. Numerous foods have antioxidant properties and many mechanisms may be involved.

COVID-19 and oxidative stress

There are three stages of COVID-19: (i) a viral infection which lasts for one to two weeks; (ii) a second phase characterized by an intertwined cytokine and oxidative stress storm² independent of infection; (iii) a recovery phase that may last for some months⁵. The oxidative stress storm has been associated with many of the serious clinical features of COVID-19, in particular lung injury.

Many foods have antioxidant properties and several mechanisms may be involved in the control of COVID-19. However, the activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) anti-

oxidant transcription factor may be of primary importance among other antioxidant mechanism. ^{2,6,7} Differences in COVID-19 death rates among countries may partly be associated with nutrients activating Nrf2 such as fermented vegetables that could reduce COVID-19 severity ^{1,2,8}.

Many Nrf2-interacting nutrients, such as spices, are TRPA1 (transient receptor potential ankyrin 1) and TRPV1 (transient receptor potential vanillin 1) agonists ⁹ and channel desensitization may be a novel mechanism involved in the diet hypothesis.

TRP (transient receptor potential) channels

It has been suggested that at least three TRP channels may play a role in COVID-19: TRPA1 desensitization (papers submitted and available online ^{3,10}), TRPV1 blockage¹¹ and TRPV4 ¹². TRPA1, an excitatory ion channel highly sensitive to the oxidative stress, plays a pivotal role in augmenting sensory or vagal nerve discharges, thus evoking several COVID-19 symptoms such as cough, nasal obstruction and digestive symptoms ⁹. TRPV1 (Transient Receptor potential vanillin 1) is another possible candidate ¹³. Capsaicin is a common experimental trigger of cough through TRPV1 activation. However, TRPV1 antagonists are not very effective ¹⁴. On the other hand, a one-month treatment with oral capsaicin improves cough through a putative desensitization mechanism ¹⁵.

TRPA1 and TRPV1 are usually co-localized and demonstrate a certain interplay ¹⁶. In addition to co-expression in a subset of sensory nerves and non-neuronal cells, a functional interaction between TRPA1 and TRPV1 (synergistic effect, cross-sensitization/desensitization) has been established ^{17,18}. This suggests the cooperation between these channels to promote some of their effect. In some models, TRPV1 has regulated the desensitization of TRPA1 ¹⁸.

The pungent effect of chili and other spices is rapidly reduced by high or repeated doses ¹⁹. This was first described for capsaicin, an active component of chili peppers ²⁰. The TRPV1 receptors begin a refractory state, commonly termed as desensitization, that leads to the inhibition of receptor function ¹⁹. TRPA1 is desensitized by homologous (mustard oil; a TRPA1 agonist) or heterologous (capsaicin; a TRPV1 agonist) agonists via Ca²⁺-independent and Ca²⁺-dependent pathways in the sensory neurons ²¹. TRPA1 is desensitized by the TRPV1-Selective cannabinoid arachidonoyl-2 chloroethanolamine ²². There is a heterologous desensitization of TRPA1 via a TRPV1 pathway ^{22,23}

Another form of desensitization is 'tachyphylaxis', which is a reduction in the response to repeated applications of vanilloid ²⁴. However, a high concentration of capsaicin, applied in the nose for non-allergic rhinitis ²⁵ or on the skin for neuropathic pain ^{26,27}, can desensitize TRPV1 for weeks. It would appear that capsaicin application on the skin is safe ²⁸.

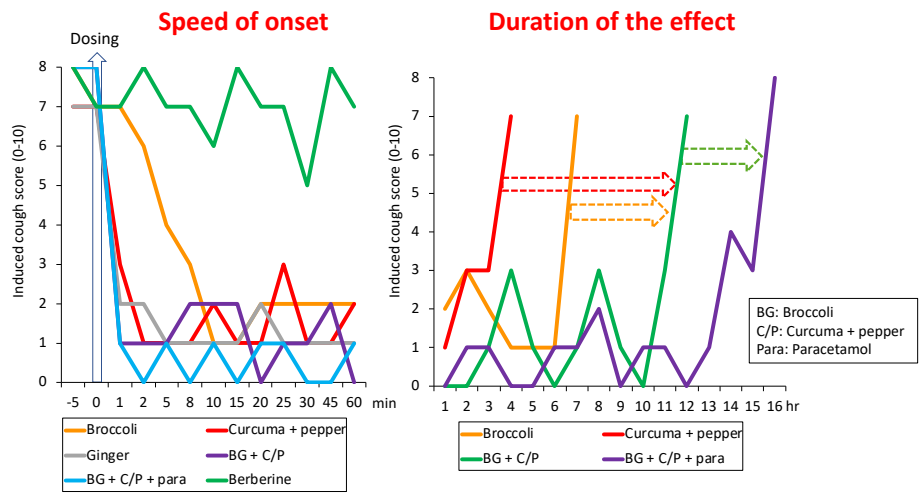
TRP desensitization by foods may occur in COVID-19

TRP desensitization has been suggested in 6 COVID-19 patients since Nrf2-TRPA1 agonists (curcuma and black pepper with broccoli capsules) reduced cough and nasal obstruction within 10-20 minutes (submitted, available online ¹⁰).

A series of cough induced challenges were carried out in one patient. Broccoli (weak TRP agonist and strong Nrf2 agonist) Reduced cough and nasal obstruction within 8-10 minutes for around 5-7n hours. Curcuma and black pepper, ginger or green tea, all Nrf2-TRPA1 agonists, improved cough and nasal obstruction in less than 2 minutes for a shorter period of time. Combining broccoli with any TRAP1 agonist increased the duration of the effect to around 10 hours. Adding low-dose paracetamol further

increased the effect to over 14 hours (papers submitted and available online ^{3,10}, Figure 1). These effects were attributed to a TRPA1 desensitization, in particular since paracetamol metabolites are TRPA1 agonists ²⁹. However, TRPV1 desensitization was not excluded as the nutrients are also TRPV1 agonists.

Figure 1: Open induced cough challenges in a single patient (from ⁹)



In order to investigate a possible TRPV1 desensitization in the same patient, four induced cough challenges were performed using low-dose oral capsaicin (10 and 30 mg of Cayenne pepper in capsules). The four challenges with capsaicin resulted in similar effects with a rapid decrease in induced cough (1-2 minutes) and nasal obstruction. The duration of the effect was around 2 hours with capsaicin 10 mg and 3 hours with 30 mg. At the end of the challenge, when cough and nasal symptoms re-appeared, the patient experienced gastroesophageal discomfort for around one hour. During the course of the challenge the patient had 5-7 identical episodes with laryngo-tracheal pruritus, one or two coughs and some nasal obstruction. These episodes did not last for more than 1-2 minutes.

The overall results of the challenges suggest a rapid TRPA1/TRPV1 desensitization that does not last long. In favour of this mechanism, the following points may be noted: (i) the ultra-rapid clinical effect is similar to challenges already carried out with curcumin and black pepper (N=6), ginger (N=3), green tea (N=4), TRPA1 agonists, or with capsaicin (TRPV1 agonist); (ii) the duration of action of the TRPA1 and TRPV1 agonists is relatively short; (iii) the episodes of cough suggest a receptor sensitization-desensitization; (iv) gastroesophageal symptoms are experienced when cough re-occurs at the end of the challenges.

These results cannot be taken as formal evidence. However, they have contributed to developing a proof-of-concept for the hypothesis that combined Nrf2-TRPA1 foods may be beneficial for some COVID-19 symptoms and that there is a synergy between Nrf2 and TRPA1 agonists.

Kimchi, a possible food prototype for the control of COVID-19

Low COVID-19 death rates in Asian countries may have been partially favoured by the traditional consumption of fermented vegetables and spices. Different types of fermented foods such as chongkukjang, doenjang, ganjang, gochujang, and kimchi are widely consumed in north eastern Asian countries including South Korea. Among them, kimchi is the most popular Korean traditional food. Kimchi is prepared by fermenting baechu cabbage with other vegetables ³⁰. The main ingredients of

kimchi are cruciferous vegetables and other healthy functional foods such as garlic, ginger, red pepper powder and scallion, all added as sub-ingredients to enhance taste, flavour, nutritional value and texture ³¹. Cabbage and cruciferous vegetables contain precursors of sulforaphane, the most active natural activator of Nrf2, whereas many sub-ingredients are TRPA1 and TRPV1 agonists. Many bacteria are involved in the fermentation of kimchi. However, lactic acid bacteria (LAB) become dominant, while the putrefactive bacteria are suppressed during salting and fermentation ³¹. LAB possess an oxidative stress tolerance and antioxidant capacity ³², and are potent Nrf2 activators ³³.

Koreans consume around 100 g of Kimchi per day ³⁰. A long-standing desensitization to TRPs is therefore possible in people eating such an amount of fermented vegetables and spices associated with an inhibition of oxidative stress through Nrf2 and TRPs.

Might a rapid and long-lasting TRP desensitization be an option in COVID-19?

Before any conclusions can be drawn and these foods recommended for COVID-19, these data warrant confirmation. In particular, the benefits of the foods need to be assessed in more severe and/or hospitalized patients, through large and properly designed studies with a double-blind, placebo-controlled design.

It will also be of importance to assess in which phase of COVID-19 they may be effective (Table 1). Nrf2 may possibly be more important in the infection phase ³⁴ whereas TRPs may target more specifically the second and third phases with a synergy with Nrf2. It is interesting to note that most, but not all, nutrients are interacting with Nrf2 (agonist), TRPA1 (usually agonists) and TRPV1 (usually agonists).

Table 1: Putative effect of Nrf2- interacting nutrients in COVID-19 phases

	Mechanism	Infection by SARS-CoV-2	Oxidative/cytokine storm	Recovery phase
COVID-19 phase		1	2	3
Sulforaphane	Nrf2	+++	+ / +++ (reduces oxidative stress and synergy with TRPs to increase duration of action)	
Allyl isothiocyanates	TRPA1		+++ (fast but short-lasting effect, synergy with sulforaphane to increase duration of action)	
Capsaicin	TRPV1		+++ (fast effect, duration of action unknown)	

Capsaicin applied on the skin or in the nose is a safe treatment, blocking TRPV1. Since there is a cross-reactivity between TRPA1 and TRPV1 for the desensitization of TRPA1, it would be of interest to conduct a proof-of-concept study to test whether capsaicin might help to reduce COVID-19 symptoms.

A single food is not a potent agonist for all three Nrf2, TRPA1 and TRPV1 pathways. However, in the diet, combinations of foods can have these three properties as it is the case for Kimchi. Optimization of foods or their active components to reduce COVID-19 may be of relevant importance.

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