

Oral capsaicin induces a very fast improvement in COVID-19 symptoms suggesting TRPV1 channel desensitization

Three stages of COVID-19 have been described: (i) a viral infection which lasts for one to two weeks; (ii) a second phase characterized by an intertwined cytokine and oxidative stress storm (iii) a recovery phase that may last for some months. Many patients during the recovery phase suffer from persistent cough. Although the cough mechanisms have not been well defined in COVID-19, they could be associated with TRP (transient receptor potential) channels.

TRPA1 (Transient Receptor potential ankyrin 1) has been proposed to be activated as it is a sensor of oxidative stress and may be associated with many COVID-19 symptoms including cough (submitted, available online ¹). TRPV1 (Transient Receptor potential vanillin 1) is another possible candidate ². Capsaicin is a common experimental trigger of cough through TRPV1 activation. However, TRPV1 antagonists are not very effective ³. On the other hand, one-month treatment with oral capsaicin improves cough through a putative desensitization mechanism ⁴.

TRP desensitization was suggested in 6 patients with COVID-19 since TRPA1 agonists (curcuma and black pepper with broccoli capsules) reduced cough and nasal obstruction within 10-20 minutes (submitted, available online ⁵). A series of cough induced challenges were carried out in one patient. Curcuma and black pepper, ginger or green tea improved cough and nasal obstruction in less than 2 minutes (Bousquet et al, in preparation, summary online). These effects were attributed to a TRPA1 desensitization but TRPV1 desensitization was not excluded as the nutrients are also TRPV1 agonists.

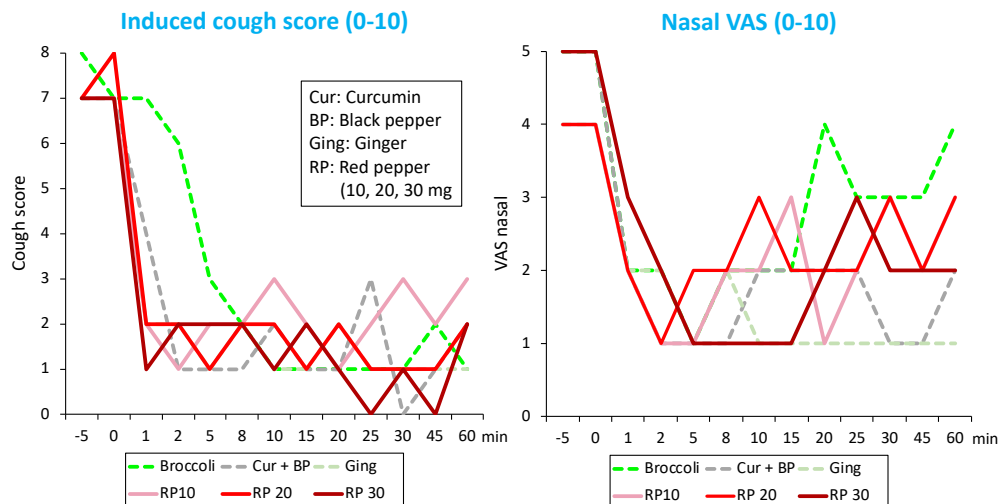
In order to investigate a possible TRPV1 desensitization in the same patient, four induced cough challenges were performed using low dose oral capsaicin (10 and 30 mg of Cayenne pepper in capsules). The challenges were performed similar to the FEV₁: the patient took the deepest breath he could, exhaled as fast and as hard as possible and counted the number of coughs. The follow up was carried out until the patient experienced spontaneous cough (VAS_{cough}≥7) or a cough score ≥7 during the challenge. This cough challenge has been largely studied in the same patient who performed 58 challenges with different compounds, some of them being ineffective. Eight challenges were done in a placebo-controlled fashion with broccoli to assess differences between active and placebo treatment ⁵ and 18 open labelled challenges were also carried out with broccoli to assess reproducibility.

The four challenges with capsaicin found similar effects with a rapid decrease in induced cough (1-2 minutes) and nasal obstruction (Figure 1). The duration of the effect was around 2 hours with 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 more than 1-2 minutes.

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

Research should confirm these data and mechanism of great importance in order to develop medications, patch tests (capsaicin), nasal sprays or food supplements based on TRPA1 and TRPV1 for the treatment of COVID-19.

Figure 1: Efficacy of oral capsaicin in induced cough challenges



References

1. Bousquet J, Czarlewski W, Zuberbier T, et al. Potential control of COVID-19 symptoms by Nrf2-interacting nutrients with TRPA1 (transient receptor potential ankyrin 1) agonist activity. <http://www.wga2lennet> 2020.
2. Bonvini SJ and Belvisi MG. Cough and airway disease: The role of ion channels. *Pulm Pharmacol Ther* 2017; 47: 21-28. 2017/07/04. DOI: 10.1016/j.pupt.2017.06.009.
3. Khalid S, Murdoch R, Newlands A, et al. Transient receptor potential vanilloid 1 (TRPV1) antagonism in patients with refractory chronic cough: a double-blind randomized controlled trial. *J Allergy Clin Immunol* 2014; 134: 56-62. 2014/03/29. DOI: 10.1016/j.jaci.2014.01.038.
4. Ternesten-Hasseus E, Johansson EL and Millqvist E. Cough reduction using capsaicin. *Respir Med* 2015; 109: 27-37. 2014/12/04. DOI: 10.1016/j.rmed.2014.11.001.
5. Bousquet J, Le-Moing V, Blain H, et al. Efficacy of broccoli and glucoraphanin in COVID-19: From hypothesis to proof- of-concept with three experimental clinical cases. <http://www.wga2lennet/PDF/06Clinical%20cases-broccoli.pdf> 2020.

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Jean Bousquet, Montpellier, France and Berlin, Germany

Wienia Czarlewski, Levallois, France

Torsten Zuberbier, Berlin, Germany

Joaquim Mullol, Barcelona, Spain

Josep M Anto, Barcelona, Spain