Potential control of COVID-19 symptoms by Nrf2-interacting nutrients with TRPA1 (transient receptor potential ankyrin 1) agonist activity

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Abstract

In this paper, we propose that COVID-19 morbidity may be associated with TRPA1 (transient receptor potential ankyrin 1). TRPA1 induces inflammation, plays key roles in the physiology of almost all organs. It may augment sensory or vagal nerve discharges to evoke pain and several symptoms of COVID-19 including cough, nasal obstruction, vomiting, diarrhea and partly agueusia and anosmia. TRPA1 can be activated by ROS and may therefore be upregulated in COVID-19. TRPA1 can be activated by pungent compounds including many Nrf2-interacting foods. Interactions between Nrf2-associated nutrients and TRPA1 may be partly responsible for some COVID-19 symptoms. Regulation by Nrf2 is still unclear. In COVID-19, it is proposed that rapid desensitization of TRAP1 by some foods could reduce symptom severity and could provide new therapeutic strategies.

Key words: COVID-19, Nrf2, TRAP-1, broccoli, pungent foods, cough challenge

Introduction

The transient receptor potential (TP) vanilloid 1(TRPV1) and ankyrin 1 (TRPA1) are members of the TRP superfamily of structurally-related, non-selective cation channels. TRPV1 and TRPA1 are frequently co-localized in sensory neurons, and interact to modulate function. They are also expressed in many non-neuronal cells such as vascular smooth muscle, monocytes, lymphocytes, keratinocytes, epithelial cells and endothelium [1].

TRPA1, an excitatory ion channel originally found as the receptor of mustard oil in sensory neurons [2], plays a pivotal role in detecting cysteine-reactive irritants and in augmenting sensory or vagal nerve discharges to evoke pain and cough. TRPA1 induces inflammation, plays key roles in the physiology of almost all organs[3] and exhibits the highest sensitivity of TRPs to oxidants. TRPA1 can be activated by

cold, heat, pungent compounds, mechanical stimuli, endogenous signals of inflammation and oxidative stress [4]. Its function is modulated by multiple factors, including Ca^{2+}, trace metals, pH, reactive oxygen species (ROS), nitrogen, and carbonyl species. A major function of TRPV1 is the detection and regulation of body temperature [5].

There have been large country variations in COVID-19 death rates. Some very low death rate settings such as those of Eastern Asia, Central Europe, the Balkans and Africa have a common feature of eating large quantities of fermented vegetables whose intake is associated with activation of the Nrf2 (Nuclear factor (erythroid-derived 2)-like 2) anti-oxidant transcription factor [6-8]. There are many Nrf2-interacting nutrients [9] (berberine, curcumin, epigallocatechin gallate, genistein, quercetin, resveratrol, sulforaphane) that act similarly to reduce insulin resistance, endothelial damage, lung injury and cytokine storm (Bousquet et al., submitted). It has been proposed that Nrf2-interacting foods and nutrients can re-balance insulin resistance and have a significant effect on COVID-19 severity [8,10-12]. However other mechanism may also be involved.

In this paper, we examined whether (i) COVID-19 morbidity may be associated with TRPA1; (ii) TRPA1 may be involved in COVID-19 risk factors (obesity and diabetes), lung injury and endothelial damage; (iii) TRPV1 may be associated to TRAP1 in COVID-19; (iv) Nrf2, the most potent antioxidant system of the human body, may regulate TRPA1; (v) Nrf2-interacting nutrients are acting on TRPA1 and (vi) the results of three experimental clinical cases treated with broccoli capsules containing glucoraphanin that may be explained by TRPA1.

1- COVID-19 and TRPA1

1.1. COVID-19 symptoms

Several COVID-19 symptoms are associated with TRPA1.

COVID-19 is often associated with myalgia, back pain, widespread hyperalgesia and headache [13,14]. TRPA1 is involved in acute and chronic pain, and in migraine [3]. It may therefore be partly involved in some of the COVID-19 symptoms.

Cough is a major COVID-19 symptom [15] but is not necessarily associated with severity. TRPA1 is abundantly expressed on the innervations of the entire respiratory tract including the C-fibers of the trigeminal and vagal ganglia as well as the nasal, tracheal, bronchial and alveolar epithelial cells, bronchial smooth muscle cells and CD4+ T cells [16]. C-fibers largely "sense" the presence of potentially toxic inhaled irritants and toxicants. TRPA1 is a key contributor to cough [17,18]. TRPA1 represents a gateway to airway irritation and reflex responses induced by inhaled oxidants [19] and tobacco smoking [20]. However, both TRPA1 and TRPV1 mediate cigarette smoke-induced damage of the bronchial and alveolar epithelial cells via modulation of oxidative stress, inflammation and mitochondrial damage [21]. This suggests a complex regulatory role of TRAP1 in acute and chronic airway inflammation [22].

Smell and taste disorders are very common in COVID-19 [13,23-25]. TRPA1 is one of the TRP channels involved in nociception and is excited by pungent odorous substances. Associations have been observed between TRPA1 genetic variants and increased sensitivity to thermal pain stimuli or increased olfactory sensitivity [26]. The intranasal trigeminal system is a third chemical sense in addition to olfaction and gustation. In the nasal cavity, high levels of trigeminal receptor expression were found for TRPV1 and

TRPA1 [27]. The sensitivity of the intranasal trigeminal system to chemicals was found to be partly mediated by TRPA1[28].

The mammalian taste system consists of taste buds found throughout the oral cavity. TRPs fall into six subfamilies: TRPC for "canonical" (TRPC1-7), TRPM for "melastatin" (TRPM1-8), TRPA1, TRPV1-6, TRPML for "mucolipin" (TRPML1-3), and TRPP for "polycystin" (TRPP2, TRPP3, TRPP5). These TRP channels are important in gustatory processing. They are very sensitive to changes in temperature, and are activated by many compounds found in plants, often used as spices [29]. TRPA1 is mostly an acid-sensing and epithelial sodium channel [30] whereas TRVP1 is also sensitive to temperature. TRPA1 activators are generally recognized as noxious. However, foods and beverages containing TRPA1 activators are preferably consumed.

Loss of appetite is common [31] and may be severe in COVID-19. TRPA1 is proposed to play a role in food intake and satiety [32-35]. In animals, TRPA1 activation increases appetite [36].

Nasal obstruction alone is relatively common in COVID-19. In two studies, nasal obstruction was frequently reported but not correlated with olfactory dysfunction [37,38]. In rhinitis, nasal itch is related to TRPV1 [39]. Patients suffering from rhinitis exhibit a decreased threshold to the TRPA1 agonist allyl isothiocyanate (AITC). This correlates with symptoms and is resolved, in animals, after chemical destruction of the nasal sensory nerves [40-42].

Nausea, vomiting or diarrhea are relatively common symptoms of COVID-19 [31]. TRPA1 is expressed in both dorsal root ganglions and nodose ganglion neurons innervating the stomach as well as in nerve fibers of the gastric wall. Gastric administration of garlic powder containing the TRPA1-agonist allicin induces specific epigastric symptoms and gastric relaxation in healthy subjects [43].

Some other COVID-19 symptoms like fever or fatigue appear less likely to be associated with TRPA1.

1.2. COVID-19 risk factors and TRPA1

Obesity and, to a lesser extent, diabetes are risk factors for COVID-19. The importance of TRPA1 on the metabolic syndrome, obesity and diabetes is usually indirect using agonists that have multiple actions. Animal models are of importance for a more precise assessment of the mechanisms [44 45].

TRPV1 and TRPA1 have been associated with control of weight, pancreatic function, hormone secretion, thermogenesis, and neuronal function. This suggests a potential therapeutic value of these channels in obesity and diabetes [46,47]. Recently, a structurally similar molecule to cinnamaldehyde, cuminaldehyde, a TRPA1 agonist, was found to possess anti-obesity and anti-hyperglycemic properties and to activate TRPA1[48].

Cinnamaldehyde (in cinnamon) has a future potential in the treatment of diabetes and its complications [49]. A garlic supplement plays positive and sustained roles in blood glucose, total cholesterol, and in high/low density lipoprotein regulation in the management of diabetes [50]. However, these effects can be mediated by multiple pathways. As an example, cinnamaldehyde exerts its effects through its action on many multiple signalling pathways [47] including TRPA1-ghrelin [51] and Nrf2.

1.3. Lung injury

TRP ion channels are involved in lung injury. In mouse acute lung injury models, the bacterial endotoxin lipopolysaccharide (LPS) involves both TRPV1 and TRPA1 [22,52]. Ventilator-induced lung injury contributes to the mortality in patients with acute lung injury by increasing inflammation. In a rat model of ventilator-induced lung injury, a TRPA1 inhibitor significantly reduced inflammation in the lung tissues and the generation of reactive oxygen species (ROS) [53]. Unsaturated aldehydes generated during incomplete combustion - such as acroleine - are highly toxic for the lungs. TRPA1 protects against high-level acrolein-induced toxicity in mice. Mice treated with a TRPA1 antagonist were significantly protected from acrolein-induced mortality [54].

1.4. Endothelium

TRPA1 present in perivascular nerves mediates the vasodilatation of peripheral arteries in response to chemical agonists. TRPA1 is expressed in the endothelium of blood vessels exclusively in the cerebral vasculature, where its activation produces a localized Ca^{2+} signal that results in dilation of the cerebral arteries [55,56].

The endothelium is linked to the causes of some cardiovascular diseases. The activation of TRPA1 has a positive effect on atherosclerosis, but a negative effect on myocardial fibrosis and heart failure [57].

2. Interactions between TRPA1 and TRPV1

Capsaicin, the best studied TRPV1 agonist, induces cough [17,58]. It may be an option for the treatment of non-allergic rhinitis [59]. Acute respiratory distress syndrome (ARDS) is one of the major causes of mortality associated with COVID-19. It has been proposed that morbidity, severity of the disease, and underlying physiological events leading to mortality are closely linked to the TRPV1 expressing neuronal system (afferent/efferent neurons) in the lungs [60]. Capsaicin is also partly involved in smell and taste [61]. TRVP1 and TRPV4 are involved in pulmonary chemical injuries [62].

TRPA1 and TRPV1 receptors are co-expressed in vagal pulmonary C-fiber sensory nerves. The simultaneous activations of TRPA1 and TRPV1 by their respective selective agonists was far more effective than single agonists alone [63]. In a mouse model, liquiritin, a novel inhibitor of TRPV1 and TRPA1, protects against LPS-induced acute lung injury [52].

3. TRPA1 and Nrf2

3.1. TPRA1 is a sensory receptor for multiple products of oxidative stress

Oxidative stress, characterized by an imbalance between oxidants and antioxidants in favour of oxidants, leads to the disruption of redox signalling and physiological function. Redox signalling-induced changes are performed by ROS and reactive nitrogen species (RNS) [66]. ROS is a collective term that includes superoxide ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($OH^{\bullet}$), singlet oxygen ($^1O_2$), peroxyl radical ($LOO^{\bullet}$), alkoxyl radical ($LO^{\bullet}$), lipid hydroperoxide (LOOH), peroxynitrite ($ONOO^-$), hypochlorous acid (HOCl), and ozone (O_3), among others [67].

TRPA1 also functions as a sensor activated by ROS and modulated when intracellular changes in oxygen levels occur. Multiple agents produced during oxidative stress can activate TRPA1 expressed in sensory

neurons [68]. Besides ROS, TRPA1 channels are also activated by RNS, including nitric oxide (NO) [69]. Although many studies have been performed, the relevance of TRPA1 activation for cell signalling in oxidative stress is still unclear [70].

In the upper and lower airways, TRPA1 found in vagal sensory endings responsive to hypoxic conditions may serve as a rapid alarm system during abnormal oxidative conditions [70].

3.2. Nrf2

The nuclear factor erythroid 2-related factor 2 (Nrf2) is the major regulator of cellular resistance to oxidants. Nrf2 is mainly regulated by the Kelch-like ECH-associated protein 1 (Keap1). Nrf2 activation, through the canonical mechanism, is carried out by electrophilic compounds and oxidative stress, where some cysteine residues in Keap1 are oxidized. This results in a decrease in Nrf2 ubiquitination and an increase in its nuclear translocation and activation. In the nucleus, Nrf2 induces a variety of genes involved in the antioxidant defense [71]. It is possible that Nrf2 plays a major role in the modulation of TRPA1 by ROS.

3.3. Interactions between Nrf2 and TRPA1

There are few studies assessing the interactions between Nrf2 and TRPA1, and their results are sometimes conflicting. Specific signalling pathways of lung ischemia-reperfusion injury impair Nrf2-antioxidant response and activate oxidative stress in the brainstem, thereby leading to the amplification of TRPA1, likely via ROS [72]. Polysulfides (H2Sn) occur in the brain, activate TRPA1 and facilitate the translocation of Nrf2 [73]. The ablation of TRPA1 exacerbates the infiltration of activated macrophages, renal inflammation, and renal injury in mice after ischemic reperfusion injury [74]. In different animal models, neuroprotection has been observed and associated with the activation of the Nrf2 pathway via antioxidative signalling pathways [75-78]. A neuronal redox-sensing Ca^{2+}-influx channel, overexpressed in human cancer, upregulates Ca^{2+}-dependent anti-apoptotic pathways to promote ROS resistance. Nrf2 directly controls TRPA1 expression, thus providing an orthogonal mechanism for protection against oxidative stress together with canonical ROS-neutralizing mechanisms [79].

4. Activation and desensitization of TRPA1

4.1. Neurotropism of SARS-CoV-2

Coronaviruses are neurotropic. The expression of ACE2 in human neurons supports the neuro-invasive potential of SARS-Cov-2 [80]. In a human induced pluripotent stem cell (iPSC)-derived BrainSphere model, ACE2 was detected and SARS-Cov-2 was found to replicate [81]. In an animal study assessing olfactory damage, ACE2 and the protease TMPRSS2 were expressed in the sustentacular cells of the olfactory epithelium, but much less in most of the olfactory receptor neurons [82]. These results propose a dual model: direct viral invasion or a bystander injury after the infection of epithelial/endothelial cells [83].

4.2. Many Nrf2-interacting nutrients are TRPA1 agonists

Several Nrf2-interacting nutrients are direct TRPA1 activators [84]. These include some allyl isothiocyanates (pungent components of mustard, horseradish, and wasabi [2]), cinnamaldehyde from cinnamon [47], allicin (an organosulfur compound from garlic) [85], green tea polyphenols [86,87] and

three glucosinolates from *Sisymbrium officinale* (isopropylisothiocyanate and 2-buthylisothiocyanate) or moringin (4-[(α-l- rhamnosyloxy)benzyl]isothiocyanate) [88] [89]. Sulforaphane, an allyl isothiocyanate, does not appear to interact with TRPA1 but it might not have been tested adequately.

The plant polyphenol resveratrol [90] may have an agonist or antagonist effect [91]. An indirect agonist effect [92] was found via the N-methyl-D-aspartate receptor (NMDA) *in vivo* [93]. TRPA1 may serve as a downstream target of pro-nociceptive ion channels such as NMDA receptors [94].

There is a substantial overlapping of electrophilic ligands between TRPA1 and Nrf2. This suggests that the two systems might be part of the same network, with TRPA1 representing the sensory arm, and Nrf2 its biochemical counterpart [84]. However, not all Nrf2-interacting nutrients are activators of TRPA1 and mustard oil is not interacting with Nrf2.

4.3. Desensitization of TRP

The pungent effect of chili and other spices is rapidly reduced by high doses or by repeated doses [84]. This was first described for capsaicin, an active component of chili peppers [95]. The TRPV1 receptors begin a refractory state commonly termed as desensitization that leads to the inhibition of receptor function [84]. The 'acute desensitization' of TRVP1 accounts for most of the reduction in responsiveness occurring within the first few (~20) seconds after the vanilloids are administered to the cell for the first time. Another form of desensitization is 'tachyphylaxis', which is a reduction in the response to repeated applications of vanilloid [96].

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 [97]. There is a heterologous desensitization of TRPA1 via a TRPV1 pathway [98,99]. Resveratrol or AITC act as activators and desensitizers of TRPA1 channels [100]. Benzene metabolites - hydroquinone and benzoquinone - are highly reactive molecules producing ROS and causing oxidative stress. High concentrations of para-benzoquinone caused rapid activation of TRAP1 followed by a fast decline in a cysteine-dependent desensitization mechanism [101]. The contractile effect of TRAP1 in isolated mouse intestine can be induced by AITC. Repeated doses induce desensitization [102]. The electrophilic fatty acid NO_2-OA acts on TRP channels to initially depolarize and induce firing in sensory neurons followed by desensitization and suppression of firing [103]. NO_2-OA attenuates intracellular oxidative stress through Nrf2 and suppression of NADPH oxidase [104].

Although data are sometimes conflicting, interactions between TRPA1 and TRPV1 can modulate receptor desentization. Using patch-clamp electrophysiology, the co-expression and interaction of TRPA1 with TRPV1 proved to be the most critical for differential sensitization of sensory neurons for pain [105]. On the other hand, selective TRPA1 agonist (AITC) resulted in restoration of sensitivity to capsaicin TRPV1 channels (resensitization TRPV1 channels) [106]. Attenuation of experimental colitis by capsazepine (capsaicin-induced denervation CPZ) - attributed to its antagonistic action on TRPV1 - exerts its anti-inflammatory effects via profound desensitization of TRPA1 [107].

Nicotine activates TRAP1 [108]. The prevalence of smoking among hospitalized COVID-19 patients is low [109]. Although many different mechanisms are proposed, the desensitization of TRAP1 by nicotine may be one possibility. If this were the case, it would show that TRAP1 may be involved in severe COVID-19.

Sensory receptors like TRPA1 may serve as a gate-keeper in optimizing spice intake, thereby avoiding over-exposure and exemplifying the sensory and metabolic interactions of spicy nutraceuticals. In this scenario, desensitization might be an attempt in maintaining optimal intake of pungent compounds in spite of priming of the metabolising enzymes and a substantial higher and/or faster inactivation by metabolisation [84]. We propose that electrophilic ligands activate and desensitize TRAP1 and also activate Nrf2 that will reduce the activation of TRPA1 by the ROS produced by COVID-19.

4.4. TRPA1 and acetaminophen

Paracetamol (acetaminophen) has TRPA1-independent antipyretic effects [110] and TRPA1-dependent effects on pain [111]. The electrophilic metabolites N-acetyl-p-benzoquinoneimine (NAPQI, hepatotoxic metabolite) and p-benzoquinone, but not paracetamol itself, activate TRPA1 [68]. NAPQI also directly activates Nrf2 [112], and benzoquinone desensitizes TRPA1 [101]. The physiological and toxicological responses of paracetamol form a continuum coordinated by the Wnt and Nrf2 pathways. Therapeutic doses produce reactive ROS and NAPQI in the cytoplasm but result in little permanent damage [113]. At high doses, paracetamol can induce oxidative stress-mediated hepatotoxicity which is reduced by enhancing the Nrf2 pathway [114-116].

6. Rapid onset of Nrf2-interacting nutrients on COVID-19 symptoms

Broccoli seeds containing glucoraphanin capsules were tested in three experimental clinical cases of COVID-19. The first clinical case describes COVID-19 in a patient who has proposed the hypothesis of Nrf2-interacting nutrients in the prevention of severe COVID-19 symptoms. Capsules of broccoli were being taken before the onset of SARS-CoV-2 infection and were ineffective in its prevention. They were continued daily for over a month after the first COVID-19 symptoms. They were found to reduce most of the symptoms rapidly and for a duration of 6-8 hours by repeated dosing. When the patient was stable but still suffering from cough and nasal obstruction when not taking the broccoli capsules, a double-blind induced cough challenge was carried out to assess the speed of onset of the broccoli capsules (less than 10 minutes). A second clinical case with lower broccoli doses carried out during the cytokine storm confirmed the clinical benefits already observed. A third clinical case at the onset of COVID-19 symptoms showed similar effects. In the first clinical trial, a dose of under 600 micromoles per day of glucoraphanin was used, and trials with doses of up to 800 micromoles daily have been reported. However, such a high dose may induce some pharmacologic effects that must be investigated carefully before any study is carried out. Thus, these experimental clinical cases represent a proof-of-concept to confirm the hypothesis that Nrf2-interacting and TRPA1-agonist nutrients are effective in COVID-19. However, they cannot be used in practice before more safety data are available, and should be confirmed by proper trials on efficacy and safety. However, the detailed analysis of the cases supports TRPA1 involvement.

1- In the 3 patients, and for all ingestions of 300 mg broccoli capsules (N=46), cough (N = 39/43, 90.7%) and nasal obstruction (N = 33/38, 86.8 %) disappeared within ten minutes, and often earlier. When there was nausea, it also disappeared immediately. These rapid effects suggest TRAP1 desensitization.
2- There was only a small rapid effect on fever which does not appear to be associated to TPRA1.
3- The effect on fatigue was clear in the first case when higher doses were given at the beginning of the survey.

4- Before ingesting the broccoli capsules, anosmia and an almost complete loss of taste were observed in cases 2 and 3. After the first ingestion of broccoli, these symptoms were reduced variably and often delayed by one to 3 hours. The role of TRPA1 is unclear.
5- Cough and fever re-occurred after 6-8 hours in 43/46 the three patients. This was often associated with nasal obstruction (N = 38/46, 82.6%) and fatigue (N = 25/46, 54.3%).
6- In the 3 patients, paracetamol (250 to 1,000 mg) always increased the duration of the effect of broccoli to up to 12 hours. This effect is in line with the activation of TRPA1 by paracetamol metabolites.
7- Several challenges were performed in the first patient. They consisted of induced cough: the patient took the deepest breath he could, and then exhaled as fast and as hard as possible to induce cough. In 16 open challenges and 8 double-blind, placebo-controlled challenges, broccoli capsules reversed nasal congestion within 2 minutes and cough within 8 minutes. It is likely that tracheobronchial receptors were primed by the cough challenge and that it took longer to reduce cough than during COVID-19. The effect persisted for 6 to 8 hours. These rapid onset effects suggest TRPA1 desensitization.
8- In open cough challenges, paracetamol increased the benefits to 10-12 hours, suggesting TRPA1 desensitization.
9- In open cough challenges with Nrf2-interacting nutrients, green tea (N=4) had a similar effect as broccoli but was shorter (1 hour). Resveratrol (N=4) had an effect on both cough and nasal obstruction from between 30-45 minutes to 4-5 hours. Berberine (N=3) did not have any effect. Green tea is a TRPA1 agonist, resveratrol indirectly activates TRPA1, whereas berberine has no published effect on TRPA1. These challenges indicate that the effect on TRPA1 is more important than on Nrf2. However, Nrf2 may block the activation of TRPA1 by ROS produced by COVID-19 and allow for a longer effect, even during the challenge.

Conclusions

Hypothetic interactions of Nrf2, TRPA1 and COVID-19 (Figure 1)

A common denominator in all conditions associated with COVID-19 appears to be the impaired redox homeostasis responsible for ROS accumulation [117]. Several mechanisms have been proposed involving, among others, the renin–angiotensin–aldosterone system (RAAS) [8] and/or endoplasmic reticulum stress [118]. These hypotheses have led to propose antioxidant approaches including Nrf2 to treat COVID-19 [8,10-12]. Antioxidants may be of interest but the clinical benefits should probably take some time, and this mechanism may be more related to medium-term treatment.

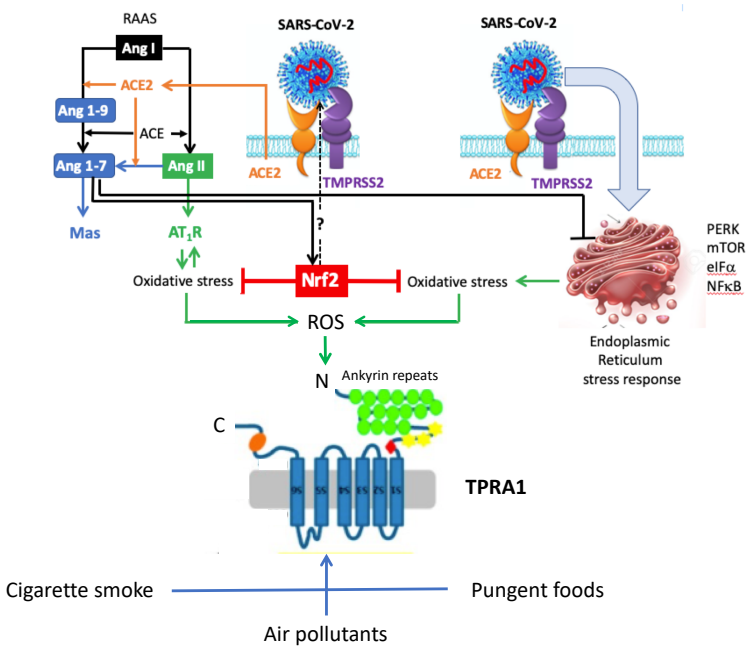
However, other hypotheses can also be proposed. TRPA1 is involved in several COVID-19 symptoms including cough, and loss of taste and smell. It can be activated by ROS and may therefore be upregulated in COVID-19. Nrf2 was found in a few studies to interact with TRPA1. Reducing ROS will most likely reduce TRPA1 hyperreactivity, thereby reducing TRPA1 activation by exogenous or endogenous agents. However, such a mechanism is likely to take time and cannot be involved in rapid onset clinical benefits.

The activation of TRPA1 by exogenous agents can lead to a rapid dose-dependent desensitization that may be effective within minutes for a few hours. This rapid onset mechanism may be sustained by antioxidants or other products.

Finally, as found for TPRV1 and capsaicin tachyphylaxis [96], a reduction in the response to repeated exposure may occur during long-term treatment. In this model, Nrf2 and antioxidants may play an important additive role in reducing ROS. This may be the case for low-death rate countries in which large amounts of nutrients interacting with Nrf2 and TRPA1 at the same time are consumed. The long-term consumption of kimchi, which contains pungent nutrients and fermented cabbage, could be the prototype.

There are several unknown issues. Two of them are the interplay between TRPA1 and TRPV1 in desensitization. The second is the regulation of these channels by oxidative stress and the role of Nrf2.

Figure 1: Interactions between TRPA1, endogenous and exogenous stimuli



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