Journal of Translational Science

Commentary ISSN: 2059-268X

Proposed mechanism for anosmia during COVID-19: The role of local zinc distribution

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The common cold is frequently associated with anosmia. A significant portion of COVID-19 patients has been reported to have anosmia and taste dysfunction [1]. A recent study from Germany found that among confirmed COVID-19 patients 47% had anosmia with a mean duration of anosmia of 8.9 days as well as an association with dysgeusia in 85% of cases [2].

There are multiple proposals for the pathogenesis of anosmia during COVID-19 including the direct and indirect toxic effect of SARS-CoV-2 on neuronal cells [3] and toxicity to non-neuronal supportive cells such as olfactory epithelium sustentacular cells, microvillar cells and olfactory bulb pericytes [4,5].

Here we propose that infections with coronaviruses including SARS-CoV-2 induce host immune responses in the nasopharyngeal mucosa; which may lead to local zinc deficiency and consequently transient anosmia and poor taste.

Zinc (Zn) is an essential micronutrient and is the second most abundant metal in the human body, with 2 to 4 grams distributed throughout the whole body. Zinc is generally taken in through food or breast milk, is absorbed via several intestinal Zn transporters, and is released into the bloodstream. It is required for cell growth, differentiation, and survival and approximately 10% of the entire human genome can potentially bind Zn through Zn-finger motifs [6]. Dietary Zn deficiency is common globally and causes thymic atrophy and depresses both innate and adaptive immune responses [7]. Zinc is a cofactor for proteins, it affects the structural and catalytic functions of enzymes and transcription factors and acts as a second messenger [8]. Zn homeostasis is tightly controlled by the coordinated activity of Zn transporters and metallothioneins and Zn itself behaves like a signaling molecule in response to extracellular stimuli.

Zinc deficiency is well known to cause anosmia and taste dysfunction. This is because one of the enzymes critical to maintain taste and smell function is a zinc dependent metalloenzyme called carbonic anhydrase (CA) [9]. Interestingly, different formulations of intranasal Zn have also been shown to cause anosmia, but the mechanisms for toxicity are complex, including oxidative stress, ATP depletion, cytoskeletal changes and apoptosis of olfactory neuronal cells, and is affected by many factors, such as concentration of zinc tested, the length of exposure, the cell type, and the presence of other toxic chemicals [10].

Myeloid and lymphoid cells manipulate intracellular and extracellular zinc metabolism via Zn binding proteins and transporters in response to immunological signals and infections [11]. Zinc is considered an acute phase reactant and Zn levels are redistributed during infection [12]. Systemic Zn deficiency is associated with decreased Th1 cytokines, interferon-gamma and interleukin (IL)-2, and unchanged production of Th2 cytokines (IL-4, IL-6, and IL-10); which causes a shift in Th1 to Th2 balance towards Th2 cytokine predominance [13].

Cellular Zn is important for viral replication, and chelation experiments have shown that decreases in Zn levels inhibit the replication of human immunodeficiency virus (HIV) and dengue fever virus [12]. Acute viral infection of the nasopharyngeal mucosa may lead to a decrease in local Zn level and this was proposed to be a part of normal host defense against respiratory pathogens [14].

Local shift in Zn homeostasis in the nose during common colds may lead to a local Th2 phenotype and may explain increased sneezing during colds. Sneezing is a protective reflex where air in the lungs is expelled out in reaction to an irritation in the nose. Sneezing may be an indicator of local Zn deficiency. Rhinovirus is the pathogen most frequently associated with common cold; once rhinovirus enters inside the nasal epithelial cell, there is no increase in the number of inflammatory cells, but neutrophils increase in the nasal mucosa and mucous secretions [15,16]. This may be due to Th 2 predominant immune responses such as kinins, leukotrienes, histamines, interleukin-1, interleukin-6 interleukin-8, tumor necrosis factor and RANTES (regulated by activation normal T-cell expressed and secreted); which can explain disease symptoms [17-19].

Early Th2 immune responses in the nasopharynx during viral upper respiratory tract infections may be protective. Th2 cytokines have also been shown to decrease the expression of SARS-CoV-2 receptor, angiotensin converting enzyme 2 (ACE-2) expression locally [20]. Reduced ACE-2 expression may be a part of host response to inhibit viral infection of neighboring cells in the nasopharynx.

Earlier studies with SARS-CoV have shown that in infected cells intracellular Zn may inhibit SARS-CoV RNA-dependent RNA polymerase (RdRp) elongation [21]. Chelation with magnesium EDTA reverses Zn effect on SARS-CoV RdRp. Zinc ions have also been shown to inhibit the proteolytic processing of replicase polyproteins in coronavirus infected cells [22].

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Key words: *COVID-19, anosmia, SARS, immune system, Th2, zinc*

Received: May 19, 2020; **Accepted:** June 04, 2020; **Published:** June 08, 2020

There is no data that show that Zn supplementation prevents viral infections, and the data on the effectiveness of Zn to treat common cold is heterogeneous [23,24]. We propose that an appropriate local host immune response to acute SARS-CoV-2 infection may include a change in nasopharyngeal Zn balance that leads to Th2 predominant immune response with reduced ACE-2 expression, sneezing, anosmia and poor taste. Nasal mucosa is in continuum with the larger mucosal system (gastrointestinal (GI), respiratory, urinary, and genital tracts) [25]. In animal models, activation of nasal mucosa by viral antigens was shown to prime the immune environment in the lungs by increasing the infiltration with activated macrophages in the absence of direct pulmonary infection [25]. Anosmia in COVID-19 patients may be an indicator of COVID-19 prognosis. Yan CH and colleagues from University of California San Diego observed that patients with anosmia were less likely to require hospitalization and that COVID-19 resolved together with the resolution of anosmia [26]. Another study from Iran suggested that patients with anosmia were less likely to have fever, cough and dyspnea compared to those without anosmia (87.9% vs 37.38%, 67.7% vs 18.98% and 18.6% vs 14.38% respectively) and hospitalization rate was low (1.1%) among patients with anosmia [27].

Data from coronavirus seroconversion studies have also shown that nasal immunoglobulin responses are important in controlling the virus replication and disease severity [28]. Data is needed on the relationship between occurrence of anosmia and nasal anti-SARS-CoV-2 immune responses as well as COVID-19 severity and prognosis. Better understanding of the mechanisms of anosmia may also help develop criteria for early anti-viral, convalescent plasma or antibody treatment.

Funding

This study was funded by MiOra public health education foundation (www.miora.org).

Conflicts of interest

There are no conflicts of interest.

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