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DISCUSSION FORUM

Comments on the Discussion Forum: Oromucosal immunomodulation as clinical spectrum mitigating factor in SARS-CoV-2 infection

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Abstract

The mammalian lactoperoxidase system, consisting of lactoperoxidase and the H_2O_2-producing enzyme duox, is our first line of defence against airborne microbes. This system catalyses the production of hypoiodite and hypoiodous acid in the presence of sufficient iodine. These products are highly efficient at destroying the H1N1 virus and the respiratory syncytial virus (RSV). Japan has not been affected as much as other nations during the COVID-19 pandemic (death rate about 10% of the United States), and we think this is due to a diet high in iodine. With this in mind, we suggest four actions to prevent SARS-CoV-2 infections. First, health professionals should study the preventative effect of increasing iodine in the diets of the aged, institutionalized, diabetics andsmokers. Second, the recommended daily intake (RDI) for iodine should be significantly increased, to at least double, the current RDI. Governments should encourage the use and distribution of cheap iodized salts, kelp and seaweed. Third, more research should be done around the physiology and the protective effects of the lactoperoxidase system. Finally, the degradation products of the SARS-CoV-2 viral particle by hypoiodite and hypoiodous acid should be characterized; portions of the damaged particle are likely to elicit stronger immunity and better vaccines.

1 | INTRODUCTION

We read the excellent presentation by Rodriguez-Argente and coauthors and wish to add some thoughts to the discussion.[1] The lactoperoxidase (LPO) system is actually the first line of mammalian, immunological defence against airborne bacterial and viral infections, including influenza and the respiratory syncytial virus (RSV).[2,3] This is not well known, and some textbooks of immunology do not even mention this system.

LPO is a haem enzyme that is extruded into human lung mucosa, nasal linings and saliva and is a critical component of innate immunity.[4] LPO is a member of a small enzyme family which includes thyroid peroxidase, important in the biosynthesis of the vital thyroid hormones T4 and T3; eosinophil peroxidase, active in mammalian defence against invading parasites; myeloperoxidase, the key enzyme of natural killer, NK, cells, also responsible for the destructive oxidation of virus particles, bacteria and some transformed cells.[5] LPO has been studied in detail at the biochemical level, and the three-dimensional structure is known at atomic resolution.[6] LPO acts using thiocyanate (SCN^-) and hydrogen peroxide (H_2O_2) catalysing these into the highly reactive product hypothiocyanite ($OSCN^-$). What is not so well known is that LPO also catalyses the oxidation of iodide into the microbiocidal chemicals hypoiodite (IO^-) and

hypoiodous acid (HOI). Hypoiodous acid is a weak acid but releases atomic oxygen or I^+, incredibly powerful oxidizing agents. The structure of LPO complexed with the I^- substrate has been solved and shows iodide ion and H_2O_2 bind at many sites including the active substrate-binding site.[6]

The products $OSCN^-$, HOI and IO^- are all *potent, non-specific and general* viracidal agents which are lethal to the influenza virus.[2] Most mammals also biosynthesize the detrimental compound H_2O_2 required for LPO function by the duox ensemble present in lung mucous.[7] The entire duox-LPO system is compartmentalized to the lung and nasal mucous linings, saliva, tears. Nature thus restricts these enzyme activities to surfaces and fluids outside living tissues.

The initial COVID-19 infection rate was surprisingly low in Japan in early 2020. Japan has not enforced a strict, nationwide lockdown despite being a densely populated country, located geographically close to the COVID-19 origin and where many people live and work in crowds. In June 2021, only about 40 000 people were infected of 125 M inhabitants with a running total of about 15 000 deaths. Even with just 60% of the populace fully vaccinated, the mortality rate is about one-twelfth of the United States.[8] The typical protein source in the Japanese diet is squid and fish and for flavouring most use kelp and seaweed, all high in iodine. Adults consume more than double the iodine than the US RDA (150 μg), and average about 413 μg/day for women and 312 μg/day for men; both well under the recommended daily upper limit of 1100 μg.[9] There is an inverse correlation between the high iodine content of the Japanese diet and the low COVID-19 infection rate, and we think this is more than a correlation but a causal relation. We suggest a reason to explain this inverse correlation—the viracidal activity of the protective LPO system present in human airways and lungs is enhanced by an iodine-rich diet. It has been shown that increasing the iodine concentration in mammalian airways enhances the LPO system performance and virus destruction.[10] In addition and very importantly, both IO^- and HOI are *non-specific,* viracidal agents; the protective activity will likely be *independent* of the SARS-CoV-2 type. Mutant forms are now dominating new, widespread infections with prediction that thousands of vicious varieties are on the horizon and are very likely to complicate our future.[11] Since the median longevity of the Japanese is the highest of any industrialized nation the long-term health effects of increasing the iodine, RDI should not be serious compared to our current situation. A study of individuals in Japan who ingested much more iodine than the recommended upper limit suggested that high iodine levels can be problematic, but for only a few people with previous underlying thyroid problems. We here propose that increasing the consumption of iodide supplements and iodine-rich foods such as kelp and seaweed, which are cheap and readily available to many billions of people, will help prevent infection.

A major problem now facing humanity is that vaccines against SARS-CoV-2 infection are currently available in developed nations for the common variants but it will take years before billions can be immunized and annual re-vaccinations to deal with new varieties may be needed. It is estimated that at least 2 billion people worldwide suffer serious iodine insufficiency. The COVID-19 pandemic has also wreaked havoc with elderly and institutionalized people, who typically have a diet deficient in iodine.[12] Additionally, nothing is known about the age dependence of LPO activity in humans which may disappear over time. Smokers of all ages have been hard hit by coronavirus. We have previously presented strong evidence that CO, a major gaseous constituent of tobacco smoke, binds to LPO at the active site thus inhibiting enzyme activity.[13] Inactivation of this key enzyme correlates with the higher mortality among smokers from lung infections of all types. Unfortunately, many people will remain susceptible and will die in countries which cannot afford expensive vaccine programmes. Some countries now enforce economic shutdown with strict social distancing but in the face of political pressure these measures cannot be sustained.

Many decades ago, it was reported that povidone-iodine application to the nasopharyngeal region was beneficial against an influenza pandemic in India.[14] Recent clinical trials indicate that povidone-iodine application reduces coronavirus infections.[15] We propose a more convenient and cheaper method for containing COVID-19 by the use and distribution of iodized salt, kelp and seaweed to double or more the current iodine RDI. This simple method should encourage compliance by all but the most stubborn. We realize that increasing iodine supplementation will not completely eliminate the pandemic but should decrease the infection and transmission rates. If our simple suggestion is followed, it may have immediate and positive results for people of all cultures.

First, we hope that health professionals will study this correlation closely. Populations having diets high in iodine should display resistance against coronavirus and influenza infections in general. Studies should also be quickly performed of the preventative effect of increasing iodine in the diets of the aged and institutionalized, diabetics and smokers. Larger studies must be performed to bracket the dietary levels of iodine which when met, allow humans to best avoid coronavirus infections.

Second, we encourage health professionals to consider recommending increasing, doubling the RDI, by either use of iodized salts or increased availability of cheap seafood including kelp and seaweed. Small tablets are easily manufactured and distributed without the strict and expensive requirements of medical products. Such measures can be quickly instituted by many organizations, especially in low-income nations and the positive effects should be observed immediately.

Third, more research into the physiology of LPO needs to be done including the age dependence of LPO activity and concentrations in human airways. Like many human enzymes, there may be several isomeric forms of LPO; some with higher and some with lower activities, some expressed more than others. Study should be made of the genetics of LPO and the duox enzymes to uncover possible multiple forms. On the positive side, the resistance of COVID-19 variants to the LPO system can be easily studied using the in vitro assay techniques already made public.[2] Health professionals can be quickly informed of the relative resistance of these mutants to iodine supplementation. There must exist a mechanism for the delivery of the LPO system components from lung tissues to the mucous lining. It is likely that special transport enzymes are involved in this activity which should be discovered and characterized. Defects are likely to have dire consequences for the defence of some humans against airborne microbes.

Fourth, the structures of LPO complexes with several iodide ions and H_2O_2 have been recently published[6] so elucidation of the active LPO-HOI complex should be undertaken to better understand the actions of the protective duox-LPO-iodine ensemble. It is extremely important that the oxidation products of the SARS-CoV-2 viral particle by hypoiodite and hypoiodous acid be characterized. It is likely that many breakdown particulates make their way from the mucous lining into lung tissues where these elicit both immune and inflammation responses. Perhaps some of these particulates could be used to develop better, more broad-spectrum and longer-lasting vaccines.

The lactoperoxidase system is the first line of mammalian defence against many airborne pathogens. It is probable that increasing iodine supplementation will enable the lactoperoxidase system to more effectively destroy invading influenza viral particles, including SARS-CoV-2. Agencies and governments should encourage the use and distribution of cheap iodized salts, kelp and seaweed to this end. Studies across cultural and geographical borders should be done to better understand the protective activities of the lactoperoxidase system as a function of dietary iodine.

CONFLICT OF INTEREST

There are no competing interests.

DATA AVAILABILITY STATEMENT

Data sharing not applicable – no new data generated.

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