Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Medical Hypotheses 144 (2020) 110207

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Letter to Editors

Nasal lavage containing Angiotensin-Converting Enzyme-2 agonist can prevent and reduce viral load in COVID-19

ARTICLE INFO

Keywords:
Angiotensin-Converting Enzyme-2
Anosmia
Nasal lavage
Olfactory pathway
SARS-CoV-2

ABSTRACT

COVID-19 has been the talk of the year 2020, taking many lives and leaving others in critical conditions. It has clearly and severally been reported that the SARSCoV-2 uses the Angiotensin Converting Enzyme-2 receptors to penetrate and infect cells. Reports have also stated that the nasal and olfactory mucosa are overloaded with these receptors. We emphasize that anosmia in COVID-19 is secondary to the binding of the SARSCoV-2 to Angiotensin Converting Enzyme-2 receptors on the olfactory mucosa. A hypotheses pertaining to the presentation, diagnosis, management and possible prevention of SARS-CoV-2 is proposed. Given the high false negative rates of the polymerase chain reaction (PCR) tests, we suggest that COVID-19 negative patients with anosmia without any other nasal symptom should raise a high index of suspicion and should be further evaluated.

We propose the formulation and use of Angiotensin Converting Enzyme-2 receptors agonist or angiotensin receptor blockers (ARBs) as nasal lavage, to reduce the viral load of confirmed positive patients, and as a mode of prevention, especially in high risk patients, until a vaccine is developed. These medications are readily available and testing this theory involves determination of the correct dosage of angiotensin receptor blockers or ACE inhibitors (via dilution in water) that can be used as nasal lavage and performing efficacy trials. Potential side effects to be monitored for include low blood pressure or changes in heart rate. Administration of a medicated nasal lavage may be easier and rapidly disseminated on the nasal mucosa.

Introduction

The correlation between chemosensory changes and COVID-19 is not new, as Cooper et al. described in their recent comprehensive review that highlights the unique neurological expression of this virus [1]. Based upon this concept, alterations in diagnostics and treatment may be necessary. Herein we build on the premise of the causes of these chemosensory alterations and propose a treatment and preventive method for COVID-19. We hypothesize that the use of nasal lavage containing agonists for receptors of Angiotensin Converting Enzyme-2 (ACE-2) or Angiotensin Receptor Blockers (ARBs) which will competitively inhibit SARS-CoV-2 binding to the nasal and/or olfactory mucosa will be of great value in reducing the viral load of already infected patients and also, in preventing infection in high risk groups.

The hypothesis

Association between Angiotensin-Converting Enzyme-2 and SARS-CoV-2

The SARS-CoV-2 pandemic has claimed many lives globally, leaving hundreds of thousands of people in critical condition. This new betacoronavirus demonstrates genomic similarities to SARS-CoV-1 and MERS-CoV [2]. Clinical similarities include the type of tissues affected, morbidity due to acute respiratory distress syndrome (ARDS), and Angiotensin-Converting Enzyme-2 (ACE-2) as the primary receptor for target cell entry [3]. Unlike SARS-CoV-1, SARS-CoV-2 has approximately 4 times more affinity for Angiotensin Converting Enzyme-2 (ACE-2) receptors [4].

Angiotensin Converting Enzyme-2 (ACE-2) is a membrane-bound aminopeptidase that degrades angiotensin II to angiotensin 1–7, attenuating the effects of angiotensin II on fibrosis, vasoconstriction and sodium retention [5,6]. The association between ACE-2 and penetration of the coronaviruses into vital epithelial cells of the lungs has been extensively described in the literature [7–12]. Invasion of cells by the SARS viruses has two effects: it inhibits the activity of ACE-2 and decreases the expression of ACE-2 in infected cells. Inhibition of the conversion of angiotensin II to angiotensin, causes accumulation of angiotensin II promoting fibrosis, apoptosis and activation of inflammatory cascade [3,10]. ACE-2 receptors are broadly expressed in the nasal/oral mucosa, and respiratory epithelium [7], as well as on neurons with a suspected role in neurodegeneration [13]. One may infer that this prominent presence provides fertile ground for invasion by viruses like SARS-CoV-2.

SARS-CoV-2 primary transmission is via inhalation of particles like aerosols/droplets, or via direct inoculation through contact with infected surfaces. Over ninety percent of the virus is transmitted through the nasal mucosa including the ocular route, via drainage of tears through the nasolacrimal duct into the nasal cavity. Generally beginning in the epithelium of the upper respiratory pathway, it multiplies [2], before spreading inferiorly to the alveoli of the lungs [9], explaining the effect on adjacent olfactory mucosa. Fig. 1 is a schematic description of the interaction between SARS-CoV-2 and ACE-2 in the human body.

Up to fifty seven percent of infected patients are asymptomatic [14], those who are, vary in severity, some requiring hospitalization and intensive care. Case reports from both China and Europe reported an absence of nasal symptoms like rhinorrhea and nasal congestion, while isolated cases of rhinorrhea support the possibility of underlying chronic nasal pathologies.

https://doi.org/10.1016/j.mehy.2020.110207
Received 30 July 2020; Accepted 18 August 2020
Available online 24 August 2020

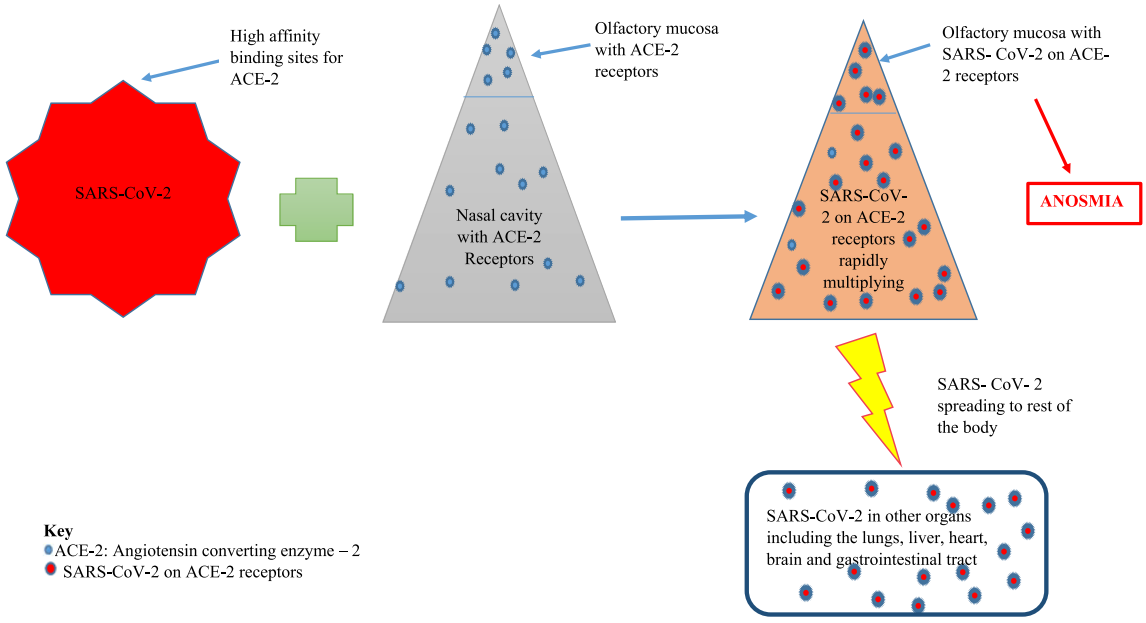

Fig. 1. Schematic description of the interaction between SARS-CoV-2 and ACE-2 receptor showing multiplication in the nasal mucosa and spread to the rest of the body.

Angiotensin-Converting Enzyme-2 (ACE2) expression

Vast distribution of ACE-2 receptors may explain the multi-organ targeting of SARS-CoV-2. Human studies demonstrated ACE-2 receptors expressed in over fifteen different organs including endothelial cells from small and large arteries and veins, nasal and oral mucosa, as well as endothelial cells of the brain [7]. Furthermore, there is increased staining of ACE-2 in olfactory mucosal epithelial biopsies [15].

It has been suggested that SARS-CoV-2 is capable of invasion of the Central Nervous System (CNS) through hematogenous spread or via retrograde neuronal route. Autopsy results of patients with COVID-19 demonstrated edema and hyperemia of brain tissue, and degeneration of neurons [13]. Additionally, a case of bilateral cerebral infarcts in a patient with COVID-19 has been reported [16], which one can extrapolate to ischemia at the olfactory cortex, explaining anosmia.

The olfactory system and diagnosis of anosmia

The olfactory system is composed of the olfactory epithelium, olfactory bulb in the forebrain, primary olfactory cortices, the uncus of the hippocampal gyrus, and sensory targets. Apart from the neural part of the olfactory system, the olfactory mucosa is known to contain several cell types, some of which may have ACE-2 receptors. A unique property of the olfactory system is that each neuron is directly exposed to the external environment, making them susceptible to macromolecules and neurotropic pathogens like viruses [17].

Olfaction is of paramount importance to humans, it aids in identifying and locating food, other humans or places. The sense of smell also aids in identifying hazardous odorants like gas leakages and smoke. Humans also generate pheromone-like compounds. The diagnosis of anosmia can be made via several tools exploring olfactory capacity including subjective olfactory assessment (involving the use of validated questionnaires and the Visual Analogue Scale), as well as objective tests like psychophysical, neurophysiological testing, and neuroimaging. While subjective assessment may be useful in resource limited settings, more objective testing such as the “sniffin’ sticks” test is recommended. Anosmia in the absence of rhinitis can be used as a patient-reported subjective diagnostic marker.

Association between SARS-CoV-2 and anosmia

In mouse studies, SARS-CoV-1 has already been proven to be neurotropic, entering the brain via the olfactory bulb leading to *trans*-neuronal spread, and one may infer that SARS-CoV-2 behaves similarly. The association between SARS-CoV-2 and anosmia in the literature [15,18] includes reports of anosmia appearing before, during or after the onset of general symptoms [15]. As reported by Lechien and colleagues, almost one fifth of COVID-19 patients had hyposmia/ anosmia without nasal obstruction or rhinorrhea [18]. Unlike other viruses, the unique symptom of anosmia in the absence of rhinitis and rhinorrhea in SARS-CoV-2, may be the direct result of targeted viral binding to ACE-2 receptors on olfactory neurons, without activating an inflammatory pathway. Anosmia as the predominant symptom of COVD-19 has been reported and since the virus is known to be neuro-invasive, these patients must be fully evaluated especially in the absence of other symptoms [19].

Olfactory dysfunction is described according to the anatomical location of the inciting lesion as follows: conductive dysfunction (blockage of odorant transmission to the neuro-epithelium), sensorineural dysfunction, (damage or loss of olfactory neuro-epithelium or nerve) or central dysfunction (damage or loss of olfactory processing pathways in the CNS). We hypothesize that in SARS-CoV-2, the causative route is multifactorial. Conductive dysfunction due to the binding of the virus to ACE-2 receptors present on olfactory receptors, while sensorineural and central dysfunction secondary to the neurodegenerative effects of the virus [1,13]. Furthermore, secondary multisystem viremia, occurring following viral replication in the respiratory tract may also affect the olfactory pathway via ACE-2 receptors or via resultant cerebral infarcts [16].

In SARS-CoV-1, a strong association was found between viral loads and the disease severity [20], we can infer a direct relationship between viral loads and the severity of olfactory dysfunction in SARS-CoV-2. Duration of the hyposmia/ anosmia is varied with reports of 25–56% improvement within one to two weeks following resolution of general symptoms [18]. This return of olfaction is directly correlated to eradication of the virus from the olfactory epithelium. However, in the case of damage of olfactory receptor neurons, an average of ninety days maybe required for their regeneration.

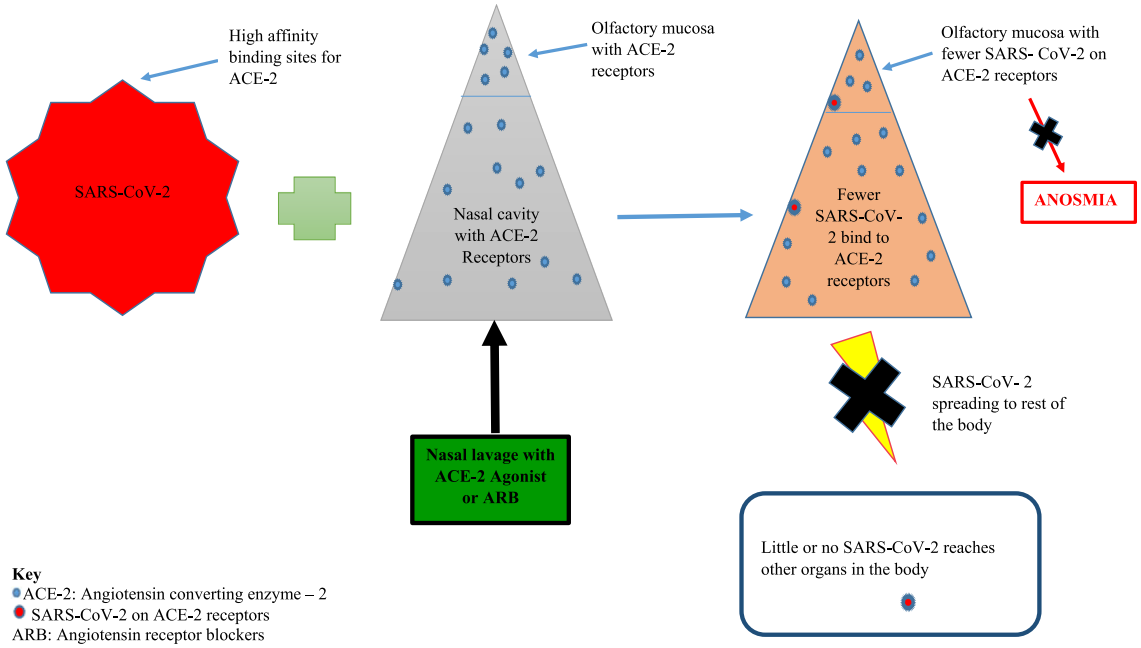

Fig. 2. Schematic representation of the effect of Nasal lavage with ACE-2 agonist or ARB on the nasal mucosa, showing a reduction in viral multiplication and spread.

Evaluation of the hypothesis

We suggest a pharmacological approach to reduce infectivity using nasal lavage containing agonists for receptors of ACE-2 or Angiotensin Receptor Blockers (ARBs) which will competitively inhibit SARS-CoV-2 binding. Other competitive inhibition of receptor binding with ACE-2 has already been suggested for the management of patients with pulmonary symptoms [12]. The potential application of soluble ACE-2 as a decoy to bind the virus thereby sparing cellular ACE-2 has already been advocated [16]. A recombinant human ACE-2, GSK2586881 has been tested through phase one and phase two studies with favourable results in patients with Acute Respiratory Distress Syndrome [11]. Recent reports found that hypertensive COVID-19 positive patients treated with Angiotensin Converting Enzyme inhibitors (ACEIs) or angiotensin receptor 1 antagonists were less likely to develop severe disease [16]. Studies demonstrated effective use of ACEIs and angiotensin receptor antagonists to mitigate the deleterious effect of elevated angiotensin II on pulmonary fibrosis.

This may be extrapolated to a nasal lavage inhibiting the binding of SARS-CoV-2 viral domain to ACE-2 receptors in the nasal mucosa. ACE-2 is strongly pH dependent under acidic conditions, being almost inactive at pH 5.0, with optimal activity at or above a pH of 6.5 [5], an important consideration in the formulation of any nasal wash. Fig. 2 is a schematic representation of how the introduction of nasal lavage reduces the viral load in the nasal mucosa, thus, reducing the spread to other organs.

Testing this theory will involve the determination of the correct dosage of angiotensin receptor blockers or ACE inhibitors (via dilution in water) that can be used as nasal lavage and performing efficacy trials. Potential side effects to be monitored for include low blood pressure or changes in heart rate. Administration of a medicated nasal lavage may be easier and rapidly disseminated on the nasal mucosa. As far as the device to be used to deliver the lavage, it has been established that, to allow the best irrigation of the whole nasal cavity, compressible douching systems should be used. In adults, they should allow a minimum output pressure of 120 mbar, a good connection to the nostril, a possible insertion into the nasal vestibule, and an irrigation stream directed upwards at about 45° [21].

Consequences of the hypothesis and discussion

To date, there exist no definitive cure and no means of immunization, the consequence of which is continuous fear of contagion, economic instability and depreciation in international relations worldwide.

With a high false negative rate of rapid polymerase chain reaction (PCR) testing [22], a high index of suspicion should be raised for those patients presenting with negative PCR and anosmia, and olfactory testing may help to positively identify them. Furthermore, those with severe anosmia potentially may have a more severe disease course.

The use of nasal lavage will certainly reduce the viral load in the nasal mucosa of infected patients and secondly, prevent the acquisition of COVID-19 until a full vaccine is developed. This may be particularly beneficial for those patients at high risk including elderly, immunodeficient patients, oncological patients and those with significant comorbidities. We hypothesize that the development of this nasal lavage can help to contain this virus and will markedly relieve the world of this load inflicted by the COVID-19.

Funding

No funding was received for this manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110207.

References

[1] Cooper KW, Brann DH, Farruggia MC, et al. COVID-19 and the Chemical senses: supporting players take center stage. Neuron 2020;107.
[2] Lu R, Zhao X, Li J, et al. Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet

2020;395:565–74.
[3] Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: Molecular mechanisms and potential therapeutic target. Intensive Care Med 2020;46(4):586–90.
[4] Walls A, Park YJ, Tororici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-Cov_2 spike glycoprotein. Cell 2020;181(2):281–92.
[5] Vickers C, Hales P, Kaushik V, et al. Hydrolysis of biological peptides by human angiotensin-converting enzyme-related carboxypeptidase. J Biol Chem 2002;277:14838–43.
[6] Santos RAS, Sampaio WO, Alzamora AC, Motta-Santos D, Alenina N, Bader M, et al. The ACE2/angiotensin-(1–7)/MAS axis of the renin-angiotensin system: focus on angiotensin-(1–7). Physiol Rev 2018;98(1):505–53.
[7] Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus: a first step in understanding SARS pathogenesis. J Pathol 2004;203:631–7.
[8] Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003;426(6965):450–4.
[9] Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020;12(1):1–5.
[10] Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. Nat Med 2005;11(8):875–9.
[11] Khan A, Benthin C, Zeno B, Albertson TE, Boyd J, Christie JD, et al. A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. Crit Care 2017;21(1):234.
[12] Wong SK, Li W, Moore MJ, Choe H, Farzan M. A 193-amino acid fragment of the SARS coronavirus S protein efficiently binds angiotensin-converting enzyme 2. J Biol Chem 2004;279(5):3197–201.
[13] Li SR, Tang ZJ, Li ZH, Liu X. Searching therapeutic strategy of new coronavirus pneumonia from angiotensin-converting enzyme 2: the target of COVID-19 and SARS-CoV. Eur J Clin Microbiol Infect Dis 2020;39(6):1021–6.
[14] Day M. Covid-19: identifying and isolating asymptomatic people helped eliminate virus in Italian village. BMJ 2020; published online Mar 23. DOI: 10.1136/bmj.m1165.
[15] Chen M, Shen W, Rowan NR et al. Elevated ACE2 expression in the olfactory epithelium: implications for anosmia and upper respiratory SARS-COV-2 entry and replication. BioRxiv 2020; published online May 9. DOI: 10.1101/2020.05.08.084996 (preprint).
[16] Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. N Engl J Med 2020. https://doi.org/10.1056/nejmc2007575. published online Feb 8.
[17] Mori I, Nishiyama Y, Yokochi T, Kimura Y. Olfactory transmission of neurotropic viruses. Journal of Neurovirology 2005;11(2):129–37.
[18] Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol 2020. https://doi.org/10.1007/s00405-020-05965-1.
[19] Xydakis MS, Dehgani-Mobaraki P, Holbrook EH, et al. Smell and taste dysfunction in patients with COVID-19. Lancet Infect Dis 2020. https://doi.org/10.1016/S1473-3099(20)30293-0.
[20] Hung IFN, Cheng VCC, Wu AKL, et al. Viral loads in clinical specimens and SARS manifestations. Emerg Infect Dis 2004;10(9):1550–7.
[21] Campos J, Heppt W, Weber R. Nasal douches for diseases of the nose and the paranasal sinuses-a comparative in vitro investigation. Eur Arch Otorhinolaryngol. 2013;270(11):2891–9.
[22] Long C, Xu H, Shen Q, et al. Diagnosis of the Coronavirus disease (COVID-19): rRT-PCR or CT? Eur J Radiol 2020;126:108961.

Gaelle Vofo[a,1,*], Ronit Brodie[b], Menachem Gross[a]
[a] *Department of Otolaryngology-Head and Neck Surgery, Hadassah Hebrew-University Medical Center, Jerusalem Israel*
[b] *Department of General Surgery, Hadassah Hebrew-University Medical Center, Jerusalem Israel*
E-mail addresses: gaellefotsing@gmail.com (G. Vofo), ronitu@hadassah.org.il (R. Brodie), drgrossm@gmail.com (M. Gross).

* Corresponding author at: Department Otolaryngology-Head and Neck Surgery, Hadassah Hebrew-University Medical Center, P. O. Box 12000, Jerusalem 91120, Israel.
[1] ORCID ID: 0000-0001-7553-5155.