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Medical Bulletin

Blue Cross Division

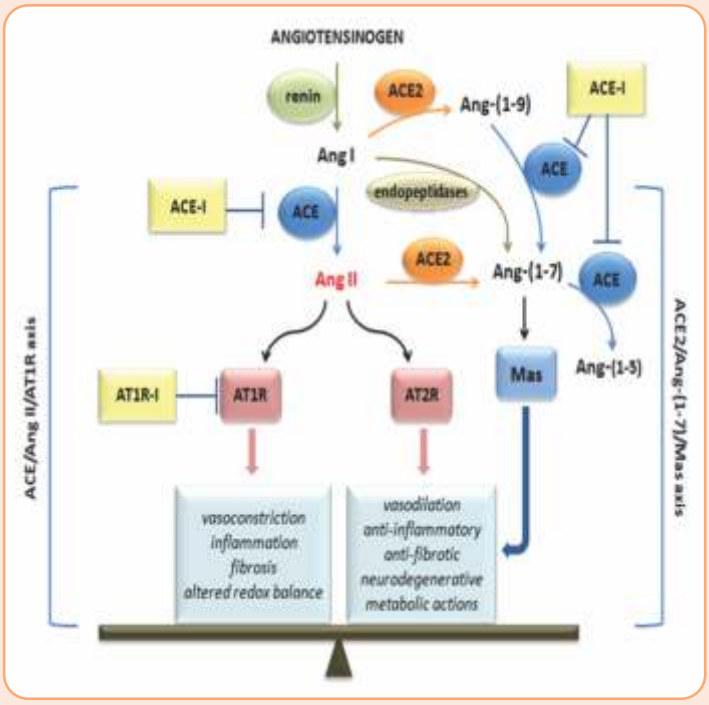
Discussions around ACE-2 RECEPTORS, ARB'S & SARS COV-2

The renin-angiotensin-aldosterone system (RAAS) is an elegant cascade of vasoactive peptides that orchestrate key processes in human physiology. SARS Cov-2 interface with the RAAS through ACE-2 enzyme that physiologically counters RAAS activation. This interaction has been proposed potential factor in the infectivity and the concerns exists about the use of ACE inhibitors & ARBs.

These concerns are based on considerations of a biological plausibility, & observation that there is an over-representation of patients with hypertension and other cardiovascular co-morbidities among patients with COVID-19 who have poor outcomes. Speculation about worse outcomes among patients on these medications during the COVID-19 pandemic has caused a widespread anxiety among patients.

What is ACE-2?

ACE-2 is a transmembrane metallocarboxypeptidase with homology to ACE, a key player in the Renin-Angiotensin system (RAS) & target for treatment of hypertension.



RAAS Physiology and ACE-2 Receptors

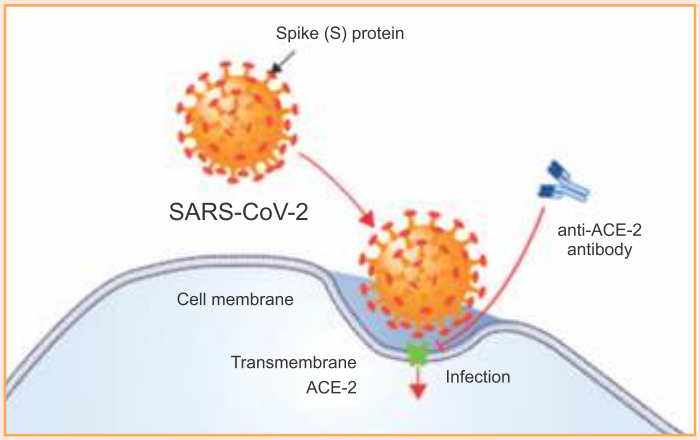
How does SARS COV-2 enter the body?

It has been well-known that SARS-CoV-2 appears to be optimized for binding to the human receptor ACE-2.

The ACE-2 receptor, located on alveolar epithelial cells, serves as a high affinity receptor and co-transporter for SARS-CoV-2 to enter the lungs. The spike (S) glycoprotein of SARS-CoV-2 virus binds ACE-2 with high affinity.

ACE-2 is expressed in a variety of different tissues including both the upper and lower respiratory tract, myocardium and the gastrointestinal mucosa.

Coronavirus enters the human cell by binding its viral spike (S) proteins to ACE-2 and on S protein priming by **TMPRSS2** (Transmembrane protease serine 2), fusing the viral and host cellular membranes.



Ace-2 receptor for SARS Cov-2 entry

How can ARBs benefit in SARS COV-2 infection?

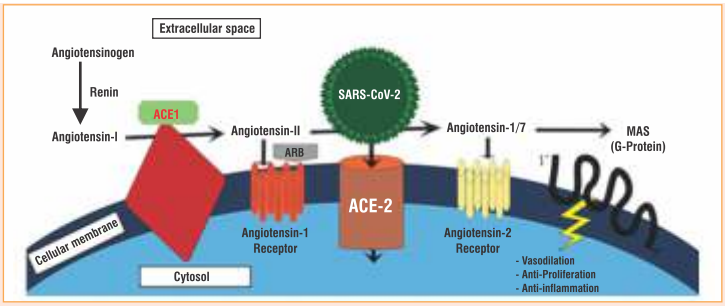
Two opposite hypotheses have been proposed for the effects of RAS inhibition with ACEIs or ARBs on the lungs (harmful vs beneficial effects).

In the **"harmful effect"** hypothesis, RAS inhibition up-regulates ACE2 expression at the cell surface, thus promoting SARS-CoV-2 entry. This ACE-2 receptor up-regulation results in increased binding sites for SARS-CoV2, leading to preferential Covid19 infection.

In the **"beneficial effect"** hypothesis, RAS inhibition reduces the production of Ang. II, which would otherwise, upon SARS-CoV-2 binding, activate AT1R, driving inflammation and fibrosis in the lung.

Researchers have proposed that inhibition of ACE may stimulate a negative feedback (given lack of angiotensin II), up regulating ACE-2 receptors & decreasing overall inflammation.

It has also been argued that use of ACE inhibitors impairs the ACE/angiotensin II/angiotensin-1 receptor pathway, leading to disruption of the ACE-2/angiotensin 1-7/MAS (MAS-related G protein-coupled receptor) pathway that could lead to decreased production of ACE-2, thereby decreasing chances of SARS-CoV-2 entering the cell.



ACE-2/angiotensin 1-7/MAS Pathway

Conclusion

- Finally, given the contradictory hypotheses, rapidly evolving nature of the disease, and social media-related hysteria, several cardiology associations (HFSA/ACC /AHA and ESC Hypertension Council) have released an official statement, strongly recommending the continuation of ACE inhibitors and ARBs for COVID-19 patient & who were previously taking these medications.

Clinical Evidence

In a multicentre Chinese study of 1128 hospitalized COVID-19 patients with histories of hypertension, 17% were taking ACE inhibitors or ARBs; the drugs were continued during hospitalization in two thirds of these patients. Mortality was significantly lower in ACE inhibitor or ARB users than in non-users (3.7% vs. 9.8%).

A multicenter retrospective study reports that among patients with COVID-19 & hypertensive, in-hospital use of ACEI/ARB was associated with lower risk of all cause mortality compared with either non-use of ACEI/ARB or use of a different class of antihypertensive agent.

Therefore, angiotensin receptor blockers (ARBs such as losartan, valsartan, telmisartan etc) can be a novel therapeutic approach to block the binding and hence, attachment of SARS-CoV-2 to ACE2-expressing cells, thus inhibiting their infection to host cells.

Source: https://www.who.int/news-room/commentaries/detail/covid-19-and-the-use-of-angiotensin-converting-enzyme-inhibitors-and-receptor-blockers; https://www.rndsystems.com/resources/articles/ace-2-sars-receptor-identified;https://www.ersnet.org/covid-19-blog/ace2-receptor-blockers--a-novel-therapeutic-approach-for-covid-19; Rico-Mesa JS et al. CurrCardiol Rep 2020; 22(5): 31; https://www.jwatch.org/na51458/2020/04/28/ace-inhibitors-and-arbs-good-bad-or-neutral-covid-19;https://www.acc.org/latest-in-cardiology/journal-scans/2020/04/24/12/22/association-of-inpatient-use-of-angiotensin; https://www.thecardiologyadvisor.com/home/topics/hypertension/treating-hypertension-and-covid-19-with-ace-inhibitors-or-arbs-may-improve-clinical-outcomes/.

Antiviral Effect of Amylmetacresol

Introduction

Respiratory tract infections (RTIs) are the most common illnesses to affect humans & most RTIs are caused by viruses with typical symptoms of sore throat, rhinitis, cough & fever. Sore throat is reported to be caused by viruses in 85-95% of cases in adults, 95% in children < 5 years & 70% in children 5-15 years.

Viruses associated with RTIs include orthomyxoviruses (influenza, paramyxoviruses (para-influenza), respiratory syncytial virus [RSV],coronaviruses, picornaviruses, adenoviruses, cytomegalovirus [CMV] & Epstein-Barr virus [EBV]). An ideal treatment would provide the symptomatic relief that patients seek as well as treat the cause. Locally delivered formats like lozenges are useful as they enable active ingredients to reach the site of infection directly.

Anti-viral properties of Amylmetacresol in RTIs

Lozenges containing Amylmetacresol (AMC) have demonstrated statistically significant reductions in sore throat symptoms in placebo-controlled clinical trials.

AMC lozenges have demonstrated antibacterial and local anesthetic/analgesic effects and have also been shown to have some anti-viral effects in vitro on three enveloped viruses - RSV, influenza A virus and severe acute respiratory syndrome coronavirus (SARS-CoV).

Mechanism of action

Phenols & cresols disrupt the lipid membranes & also cause rapid denaturation of proteins. Amylmetacresol is a phenol having structure of m-cresol & may exhibit virucidal activity. Immediate clumping because of mild denaturation of the external protein spikes with distortion of the virus morphology was detected, probably explaining the reason for its virucidal action.

Thus, the reduction of the virus infectivity in the saliva would reduce the virus transmission to others in addition to the immediate clinical benefits of reducing soreness.

In Vitro Studies

It was investigated whether AMC/DCBA lozenges had virucidal effects in vitro against two viruses associated with RTIs, parainfluenza virus (type 3) & CMV.

Virucidal effects were observed with the active lozenges & the active ingredients as free substances against both parainfluenza virus & cytomegalovirus. Mean reductions in viral titre were significantly greater compared with placebo & peak effects were observed for the shortest incubation time, 1 min. These findings suggest that AMC or DCBA lozenge have the potential to have local antiviral effects in patients with sore throat due to viral RTIs.

In another study, AMC/DCBA solution was shown to inactivate respiratory viruses influenza A, respiratory synctial virus (RSV) and severe acute respiratory syndrome coronavirus (SARS-CoV). A titre of approximately 3.5 log10 TCID50 was reduced, within 2 minutes. Extensive clumping and morphological changes in spike configuration was observed after contact with the virucidal mixture. It could be concluded that, AMC or DCBA lozenges, have significant effects in reducing the infectivity of certain infectious viruses in the throat & presumably in cough droplets, thus reducing, opportunities for person-to-person transmission.

Conclusion:

- Most RTIs are self-limiting and are caused by viruses, and do not warrant antibiotic treatment. Despite this, patients with RTIs often receive antibiotics, fuelling the rise of antibiotic resistance. Therefore, there is a need to encourage patients to try alternative non-antibiotic therapies, which ideally treat the symptoms and the cause.
- AMC or DCBA lozenges have the potential to present local antiviral effects in patients with sore throat due to viral RTIs. In addition, the lozenges have also demonstrated efficacy against sore throat symptoms in clinical trials.
- Systematic review & meta-analysis data supports the use of these lozenges as a first-line treatment for sore throat caused by viral RTIs as AMC or DCBA lozenges are well-tolerated and provide safe, fast and effective treatment option.

Source: *Morokutti-Kurz M et al. Int J Gen Med 2017, 10: 53-60; Shepherd A et.al; Antiviral Research 2015, 123: 123: 158-162; Oxford JS et.al;Int J of Clin Practice 2011: 1-20.Weckmann G et.al; Int J ClinPract. 2017;e13002;Ting Wan Tan et al, IJMPR, 2018, 6(4): 173-182.*

Vitamin D and COVID-19

With the finding of presence of vitamin D receptors (VDRs) in all the tissues, Vit.D has now a well-characterised role beyond bone health and the low levels are found to be associated with increased susceptibility to infectious diseases notably, upper respiratory tract infections.

A growing body of circumstantial evidence now specifically links outcomes of COVID-19 & vitamin D status.

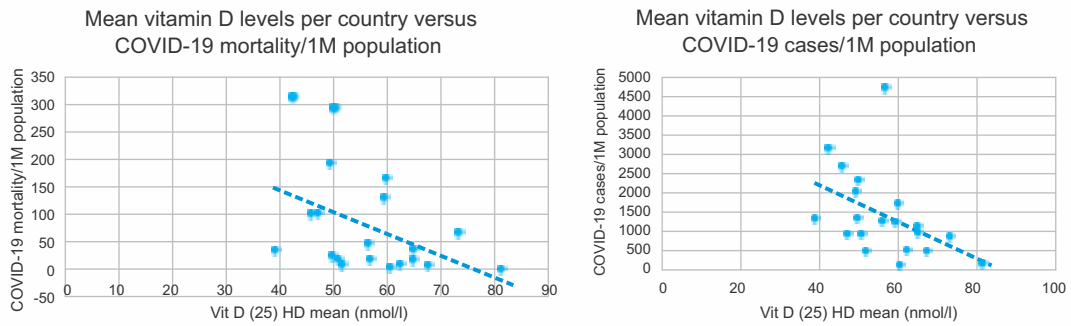
How does vitamin D play a role in SARS-COV-2 infection?

A role for vitamin D in the response to COVID-19 infection could be Vitamin D may reduce the inflammatory response to infection with SARS-CoV-2. At low levels of vitamin D the immune system becomes overactive and a phenomenon known as a cytokine storm ensues. Vitamin D has been found to modulate macrophages' response, preventing them from releasing too many inflammatory cytokines and chemokines.

Clinical evidence

"In a study it was observed that high C-reactive protein (CRP) levels were associated with the severity in COVID-19 patients, which was in turn associated with vitamin D deficiency. Hence it could be concluded based on retrospective data and indirect evidence that there could be a possible role of vitamin D in reducing complications attributed to unregulated inflammation & cytokine storm.

"A study conducted to examine the vitamin D levels in 20 European countries affected with COVID-19, it was observed that the mean vitamin D levels in each country was strongly associated with the number of cases as well as mortality rates. The vitamin D levels were observed to be severely low in the aging population especially in Spain, Italy & Switzerland, which also happened to be some of the most vulnerable group of population for COVID-19.



The study concluded that there was a significant relationship between vitamin D levels & the number of COVID-19 cases and especially the mortality caused by this infection. The most vulnerable group for COVID-19 was found to be the one with most deficits in Vitamin D.

"In another study conducted on 4314 patients that were tested for COVID-19, it was observed that the COVID-19 rates in the vitamin D deficient group were 21.6% versus12.2% in the vitamin D sufficient group, concluding association of low levels of vitamin D with increased risk of COVID-19 infection.

Recommended dose : The daily recommended dose is 1000 1U to 2000 IU depending upon the age and levels of Vitamin D. Weekly dosage of 60,000 IU for 8 to 12 weeks is advised. The goal should be to raise 25(OH)D concentrations above 40-60 ng/mL (100-150 nmol/L).

Conclusion

Vitamin D has already been shown to protect against acute respiratory infections and it was shown to be safe. Researchers thus believe that Vitamin D supplementation may help to protect against COVID-19 infection and may also prevent the severity of the infection.

Source: *Mitchell F. Lancet Diabetes Endocrine 2020; S2213-8527 (20) 30183-2;https://www.researchsquare.com/article/rs-21211/vi; https://medrxiv.org/content /10.1101/2020.04.08.20058578v4; https://www.medrxiv.org/content/10.1101/2020.05.08.20095893.*

Covid through your eyes?

Corona SARS CoV-2, is a highly contagious infection which is known to spread through droplets that enter the nose or mouth from an infected person if he coughs or sneezes.

But can it spread if the droplet enters the eyes?

So much remains unknown about the new coronavirus, SARS-CoV-2, that researchers are still trying to establish whether infection can actually happen through the eyes & it may be plausible as some research has begun in that direction.

The conjunctiva can be infected by other viruses, such as adenoviruses associated with the common cold and the herpes simplex virus & there is the same chance of infection with SARS-CoV-2 and if there are droplets that an infected individual is producing by coughing or sneezing, then the front of the eyes is directly exposed, just like the nasal passages are exposed. In addition, people rub and touch their eyes a lot which already creates vulnerability.

In order for SARS-CoV-2 to enter a cell, the cell has to have ACE-2 receptors on its surface so for the virus to latch onto it and enter the cell, & the recent research of the eye's surface cells suggest ACE-2 were clearly present on its surface cells. Also, the researchers found that the eye's surface cells also produce TMPRSS2, an enzyme that helps the virus enter the cell.

More research is needed for a definitive answer but all of this evidence together seems to suggest that there's a good likelihood that the ocular surface cells are susceptible to infection by coronavirus.

Source: https://www.medicinenet.com/can_you_get_covid-19_through_your_eyes-news.htm

WHAT'S NEW!!!

Moderna vaccine for COVID-19

Moderna Phase I mRNA-1273 vaccine development has grabbed public attention as it could be a critical element in easing pandemic related restrictions. It uses mRNA as a vaccine strategy and the antigen choice of the virus spike protein.

However, that while mRNA vaccine manufacturing is relatively straight forward and is an important consideration for a pandemic of this scale, the issue is that the mRNA may code for enough irrelevant proteins that would negatively impact immunogenicity.

It is also still challenging to identify how much neutralizing antibodies are needed for protection.

The choice of SARS - CoV-2's spike protein as the vaccine's antigen is logical, as it is shown to be immunogenic based on experience with comparable coronaviruses and the spike is an important feature of the virus life cycle as the virus uses this appendage to enter the cell and replicate. An advantage of the mRNA vaccine's synthetic manufacturing is that the spike antigen could be modified to make it even more immunogenic.

However, there are still knowledge gaps regarding whether an mRNA vaccine containing the spike protein code would be enough to offer long term protection.

The preliminary results have shown that even lower doses of the vaccine elicited an "immune response of the magnitude caused by natural infection", which substantiates the belief that mRNA-1273 has the potential to prevent COVID-19 disease.

Source: *https://www.clinicaltrialsarena.com/comment/modernas-phase-i-covid-19-mrna-vaccine-has-manufacturing-edge-but-many-obstacles-to-confirm-protection-lay-ahead.*

Are men more susceptible to COVID-19 than women?

Covid-19 has struck as a global pandemic and a striking difference has been seen in the rate of infection among the two gender. Men have been found to be more susceptible than women in contracting the infection.

WHY?

The first and foremost theory being the role of sex hormones.
Estrogen in women may be protective whereas androgens in men may worsen the Covid-19 outcomes.

New data supporting the androgen theory has come from a study in Italy, where researchers found that patients with prostate cancer being treated with androgen deprivation therapy (ADT) were less likely to become infected with COVID-19 and die from the disease than other groups, including other patients with cancer. The findings suggest that androgens somehow make the virus more virulent and that this exacerbates the severity of disease in men. Also,TMPRSS2 an androgen-regulated gene is pivotal for priming of S-protein of virus.

The studies suggest, men with prostate cancer, only 04 / 5273 patients receiving ADT developed SARS-CoV-2 infection and none of these patients died concluding patients with prostate cancer receiving ADT had a significant fourfold reduced risk of COVID-19 infections.

These theories may explain the increased susceptibility of men to develop SARS-CoV-2 severe infections when compared to women.

Source:
https://www.medicinenet.com/men_more_susceptible_to_severe_covid-19_than_women-news.htm.

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