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COMMENTARY

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Noscapine, a possible drug candidate for attenuation of cytokine release associated with SARS-CoV-2

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Abstract

Successful treatment of viral infections has proven to be huge challenge for modern medicine with the most effective approach being prior vaccination. The problem with vaccination is the time it takes to develop an effective vaccine, validate its safety and manufacture it in large quantities. Facing Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), we simply do not have the time to develop the vaccine before thousands of people die. Therefore, any treatment which can decrease the severe symptoms due to lung damage may help attenuate mortality rates. Inactivation of ACE2 during virus fusion into the host cell may be one of the underlying reasons for intense immunological reaction seen in the lung tissue. This overreaction is probably mediated through the bradykinin receptor activation. Noscapine, a medication used for the treatment of cough, has been shown to inhibit bradykinin enhanced cough response in man. As it is already marketed in a number of countries as a cough medicine, even for children, a suitable formulation with all the required licenses is available that can be rapidly utilized in preliminary trials.

KEYWORDS
ACE2, SARS-CoV-2

1 | INTRODUCTION

In a relatively short period of time, a previously unknown virus has been able to infect tens of thousands of people across the world, kill thousands more and exert great socio-economic changes in almost every country. SARS-CoV-2 has proven to be a great challenge for the health system of every nation it has invaded and with no effective antiviral agents in hand and early signs of producing a vaccine not very promising (Menachery et al., 2015) it will most likely be wreaking havoc for at least the next couple of years.

Initial data from Wuhan, the first city to be affected by the contagion, appeared to show a virus that belonged to the coronavirus families of viruses with great genetic similarity to Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) (Zhou et al., 2020). Although there is still not enough information available on the exact mode of entry of SARS-CoV-2 into human cells, early studies have shown a mechanism similar to SARS-CoV cell entry which involves ACE2 receptors (Song, Gui, Wang, & Xiang, 2018; Walls, Park, & Tortorici, 2020; Zhou et al., 2020). The SARS-CoV family of viruses express a class I fusion protein on their surface called the spike or S glycoprotein. The S glycoprotein appears to be formed by aggregation of three heterodimer proteins each comprised of an S1 and an S2 subunits. The S1 subunit forms the anchor, attaching the virus to its receptor on cell surface which is the ACE2 enzyme. Upon attachment, the S1 subunit becomes cleaved (probably by a host protease) and the subsequent conformational change in the S2 region causes a region of hydrophobic amino acids to become exposed which somehow causes the cell and virus membranes to come together, leading eventually to virus fusion. In vitro, the fusion process can be interrupted by inhibition of ACE2 binding and by interference with S2 interaction with the membrane by heparinase treatment of target cells, or addition of lactoferrin or heparin to cell culture medium (Lang et al., 2011).

It appears that the main target for SARS-CoV family of viruses, is the lungs. The clinical manifestations of this infection are: fever, dry cough, shortness of breath, decrease in lymphocyte count, drop in arterial oxygen saturation(Lake, 2020) and in SARS-CoV-2, progressive

pathological changes in the chest radiography such as bilateral ground-glass opacities with or without consolidation, (Bernheim et al., 2020; Yoshikawa, Yoshikawa, & Hill, 2009). In postmortem examination of the lung tissue of people who had succumbed to SARS-CoV infection, wide-spread alveolar damage with pneumocyte hyperplasia and accumulation of activated macrophages has been reported (Yoshikawa et al., 2009) however, these pulmonary changes had happened after clearance of the virus from the blood with no indication of secondary infection due to other agents. This temporal separation of tissue damage and virus presence, has led some workers to suggest that pathogenesis of SARS may be, in a large extent, due to excessive immune response in the host. This is supported by some studies that have demonstrated highly increased release of cytokines in the plasma of SARS patients, leading them to coin the phrase "cytokine storm" (Nicholls et al., 2003).

There are two structurally related zinc containing carboxypeptidases: angiotensin converting enzyme (ACE) and angiotensin converting enzyme 2 (ACE2). These two enzymes appear to act in diametrically opposite directions: ACE activity leads to vasoconstriction while ACE2 activity confers vasodilation, ACE activity causes release of pro-inflammatory cytokines while ACE2 activity decreases cytokine release and inflammation (Simões e Silva, Silveira, Ferreira, & Teixeira, 2013). It is suggested that under physiological conditions, the Renin-Angiotensin System maintains normal homeostasis with regards to inflammatory response, by regulating the activity of both ACE and ACE2 simultaneously (Patel et al., 2014). Evidence is gradually accumulating regarding substrates for ACE2 other than angiotensin I, such as neurotensin, dynorphine and more importantly des-Arg^{9} Bradykinin (DABK) (Sodhi et al., 2018). Studies have shown bradykinin and its major metabolite DABK to be involved in the inflammatory response. Qian et al., 2016 described a cascade for the production of bradykinin and its conversion into DABK in the airway capillaries during the inflammation in response to the presence of a pathogen. Bradykinin is produced from high molecular weight kininogen and is then metabolized into DABK by carboxypeptidase N in circulation and carboxypeptidase M at the inflammation site. DABK acts on bradykinin 1 receptors (B1R) to increase vascular smooth muscle cell growth and leukocyte accumulation. They also showed a relationship between bradykinin and DABK levels in serum of tuberculosis patients undergoing treatment. Bradykinin itself is a bronchoconstrictor whose effect has been known to be regulated by some proinflammatory cytokines. Many other studies have presented data as to the involvement of bradykinin and DABK in the inflammatory response.

As early as 1997, Amrani, Krymskaya, Maki, and Panettieri Jr (1997) showed bradykinin increased intracellular calcium levels in human airway smooth muscle cells, in culture medium. Also, TNF-alpha enhanced the effects of bradykinin. Later research has shown that infection with the SARS-CoV (Haga et al., 2008) and SARS-CoV-2 (Pedersen & Ho, 2020) caused enhanced release of TNF-alpha. Sodhi et al have shown that loss of ACE2 in the lungs, leads to accumulation of des-Arg9 Bradykinin which in turns causes activation of bradykinin B2 receptor pathway. The consequence of this receptor activation is release of proinflammatory chemokine C-X-C motif chemokine 5 (CXCL5) and subsequent neutrophil recruitment to the lungs. Therefore, SARS-CoV-2 has dual pro-inflammatory action: inhibiting ACE2 activity which means enhanced availability of DABK due to decreased metabolism and increased release of TNF-alpha which increases the effectiveness of bradykinin as a bronchoconstrictor.

Based on the evidence presented above, one can suggest that widespread pulmonary involvement in SARS-CoV infection in general (and SARS-CoV-2 infection by extension) is due to excessive activation of the immune system secondary to viral fusion. This happens as a result of the elimination of ACE2 activity due to viral spike glycoprotein binding. The extent of the resulting cytokine release determines morbidity and mortality in infected individuals. As the decrease in the activity of ACE2 cannot be remedied in itself, by decreasing bradykinin activity in other ways, we may be able to decrease the severity of symptoms in SARS-CoV-2 infection.

Very recently in a letter to the editor, Gurwitz (2020) suggested the use of angiotensin receptor blockers (ARB) as a means of decreasing the severity of pulmonary damage in SARS-CoV-2 infected patients. This was suggested on the basis of the observations that ARBs have been shown to cause an upregulation of the ACE2 enzyme and thus should improve the ACE/ACE2 axis function. The problem with this approach is that upregulation is a biochemical process involving protein synthesis and usually happens over a time period of days. So, starting therapy with ARBs after SARS-CoV-2 infection will be too late to produce appreciable ACE2 activity increase. So alternative means of decreasing bradykinin's actions may be more effective.

Physicians had noticed that a major side-effect of administration of angiotensin converting enzyme inhibitors (ACEI) was dry, persistent cough. In order to delineate the cause of this cough, in the early 2000s, a research program was started by the late Prof Massoud Mahmoudian, in the pharmacology department of Iran University for Medical Sciences. I was involved in parts of that work. We were able to show that both the ACEI-induced and FR190997-induced (a bradykinin receptor agonist) cough response in guinea pigs, was attenuated by noscapine. Also, the antitussive effect of noscapine was not reversed by naloxone, showing a lack of involvement by the opioid receptors in noscapine's effect (Ebrahimi, Zareie, Rostami, & Mahmoudian, 2003). In order to determine its clinical effectiveness in man, in another work in our department, Mooraki et al. (2005), administered noscapine to patients suffering from moderate to severe ACEI induced cough. The cough was resolved in 90% of the cases in 2–4 days thus allowing continuation of ACEI therapy. Further work showed, tentatively, the effectiveness of noscapine in protecting neuronal cells and tissues from ischemic damage and oxidative stress (Mahmoudian et al., 2015; Mahmoudian, Mehrpour, Benaissa, & Siadatpour, 2003; Vahabzadeh, Rahbar-Roshandel, Ebrahimi, & Mahmoudian, 2015) probably via the disruption of bradykinin activity.

Noscapine has little to no analgesic, sedative and/or euphoric action and does not produce other side-effects of opioids such as respiratory suppression and constipation. This is because it does not interact with the opioid receptor.

Thus, I postulate that treatment with noscapine, can help decrease bradykinin mediated cytokine release due to ACE2 inhibition by SARS-CoV-2. This, in turn, can decrease tissue damage, especially in the lungs, shorten the patients' recovery period and potentially save lives.

It is worth noting that noscapine is already available as an antitussive medicine in many countries. Because of a lack of opioid activity, it is regarded as a safe alternative to codeine or dextromethorphan. In the Netherlands, noscapine is drug of first choice in pediatrics (Sen et al., 2011). As cough is a major symptom of SARS-CoV-2 infection, antitussive administration and noscapine especially, is ethically justified, as it is safe and effective.

In addition, if the above hypothesis is correct, then continued use of ACEIs in patients infected with SARS-CoV-2 could well contribute to severity of symptoms.

CONFLICT OF INTEREST

The author declares no conflict of interest regarding the contents of this manuscript.

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