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Letter to the Editor

COVID-19, a viral endocrinological disease?

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Ever since Chinese health officials informed the WHO of the presence of 44 patients suffering from an anomalous pneumonia apparently linked with the Huanan Seafood Wholesale Market (Wuhan City) on 3rd January 2020 [1], a conspicuous number of scientific publications on COVID-19 have understandably focused either on the main clinical presentation of the novel pathological entity or the response of the immune system to its pathogenic agent, thus following in the footsteps of the established hermeneutical research approach of contemporary infectivological studies.

According to this model, multi-organ involvement and damage is the obvious consequence of a primary pathogen-immune system interaction, in which an enhanced response of the latter (exemplified by the cytokine storm) is responsible for the rich semiological constellation described in the specialized literature [2].

While attention has been paid to the role of ACE2 inhibition by SARS-CoV-2 through a tight binding mechanism, either as an ancillary or only recently as an important aspect of this disease [3,4], our view is that this very inhibition is truly responsible for the cascade of events ultimately resulting in the described clinical presentation. Building on this, we hereby propose that the commonly accepted paradigm be reversed in that the recorded immune overreaction is regarded as the mere consequence of an originally impaired endocrinological pathway, rather than a direct response to the pathogen itself.

The renin-angiotensin-aldosterone system (RAAS) is fundamental in regulating electrolyte balance and blood pressure, and its involvement in the inflammatory response in the liver, kidney, cardiovascular and respiratory systems has been clarified. The RAAS begins (Fig. 1) with the enzyme renin secreted by the juxtaglomerular epithelioid cells located in the medial layer of renal afferent arterioles in the kidney [5]. Renin cleaves angiotensinogen into angiotensin I (Ang I), which is in turn converted into angiotensin II (Ang II), a vasoactive octapeptide, by the angiotensin-converting enzyme (ACE). Ang II then exerts its biological effects by activating G protein-coupled receptors. ACE is also responsible for the degradation of bradykinin and substance P, two local pro-inflammatory and protussive peptides that can trigger the release of prostanoids and nitric oxide (NO), and induce the cough reflex [6].

In addition, ACE2, another zinc metallopeptidase and a homologue of ACE, is responsible for producing the heptapeptide Ang (1–7) by cleaving Ang II. It was recently discovered that the ACE2/Ang (1–7)/Mas receptor pathway mitigates airway inflammation [7]. When ACE2 is blocked by the SARS-CoV-2 virus this does not occur. Another example supporting a prominent anti-inflammatory role by ACE2 is provided by asthma, in which targeting this receptor has been evaluated as a promising strategy in that it can counter the effects of AT1R activation [6].

In the light of this inhibition mechanism it becomes clear that the anti-inflammatory cascade activated by ACE2 is irreversibly blocked with all the expected multisystemic negative outcomes.

In conclusion, we believe that considering COVID-19 an endocrine disorder would help scientists make sense of the non-specific response the immune system shows towards this pathogen, unlike seen in other viral infections such as influenza [8]. Future therapeutical strategies may be directed at tackling the endocrinological RAAS pathway, hence resulting in a better understanding of the nature and presentation of COVID-19. This, beside potentially beneficial clinical implications, could ultimately prove a higher interpretative platform from which medicine may contemplate this new health challenge.

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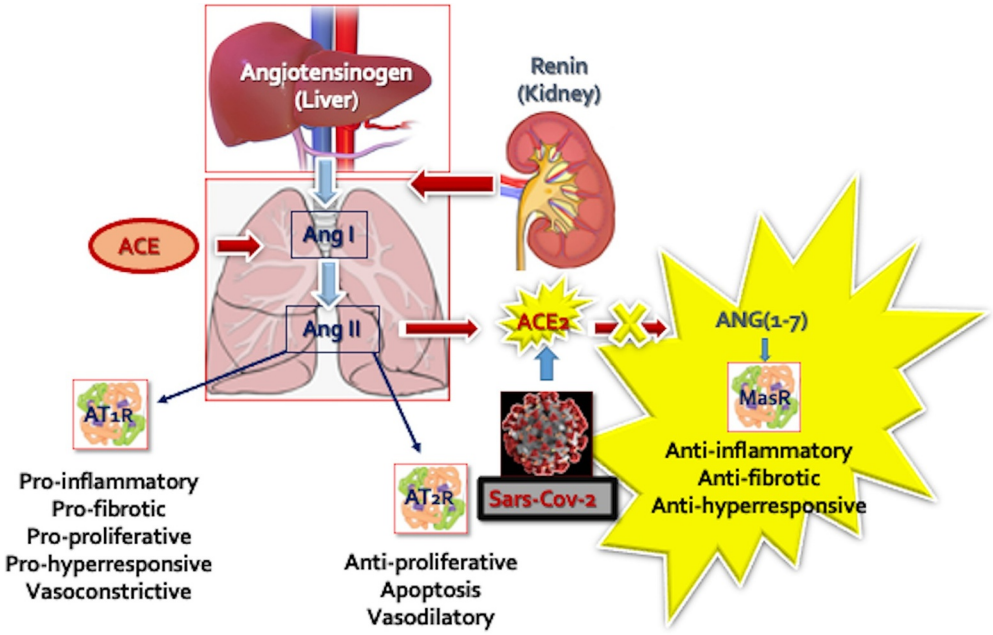

Fig. 1. Inhibition of the ACE2 enzyme by SARS-CoV-2 results in impaired production of angiotensin (1,7) which would constitutionally counter the effects of its metabolic precursor, angiotensin II, by limiting an overly inflammatory response. The drawings of organs used to create this image are in the public domain (Wikipedia). Credits: *liver*: half of the image created by BruceBlaus, CC BY-SA 4.0 (https://creativecommons.org/licenses/by-sa/4.0/); *lungs*: Patrick J. Lynch, medical illustrator; C. Carl Jaffe, MD, cardiologist, https://creativecommons.org/licenses/by/2.5/; *kidney*: modified part of an image by M.Komorniczak license: CC BY-SA 3.0 (https://creativecommons.org/licenses/by-sa/3.0/).

Declaration of Competing Interest

None.

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