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.

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Editorial

Could DIZE be the answer to COVID-19?

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A new strain of coronavirus identified as SARS-CoV-2 causes coronavirus disease-19 (COVID-19) and appeared late in 2019. The World Health Organization (WHO) classified COVID-19 as a public health emergency on 30 January 2020. The disease has been a burden on public health and has had a negative impact on the global economy. On 11 March 2020, the WHO announced it a pandemic. The angiotensin-converting enzyme 2 (ACE2) enzyme is the receptor for SARS-CoV-2 virus entry into the cell [1] and speculations have arisen on inhibiting ACE2 activity to treat COVID-19. Here, we comment on targeting COVID-19 via ACE2 activation through a small molecular compound called diminazene aceturate (DIZE).

Patients with SARS-CoV-2 virus infection develop pulmonary edema and acute respiratory distress syndrome. ACE2 is expressed in the lungs, heart, kidneys and testes [2–4], and converts angiotensin II to angiotensin (1–7) or alamandine [5–7], thus, removing the pathogenic angiotensin II from the cellular milieu [8–11]. The role of ACE2 in normal pulmonary and myocardial physiology is well established, considering ACE2 reduction leads to myocardial [12,13] and pulmonary disease [14,15]. Therefore, it stands to reason that SARS-CoV-2 could be inhibiting ACE2 activity, leading to worsened outcomes. Indeed SARS-Cov-2 virus has a higher affinity to ACE2 than SARS-CoV-1 [16]. Recently, opinions based on no evidence have been published suggesting that medications increasing ACE2 activity might worsen outcomes [17], and that patients on ARBs or ACE inhibitors pose a theoretical risk for worsened disease [18], and recently the authors have maintained their opinion [19] even after a counterargument [20]. Yet, if true, this opinion would disregard all the scientific data showing a benefit for ACE2 in pathologies. Recently, two articles [21,22] clearly pointed to a benefit of using such medications, and that there is no evidence that an increased ACE2 expression would imply an increased risk of infection or outcomes. Indeed, the authors point to elevated cellular levels of angiotensin II, as the main proponent of disease outcomes, and thus removing this peptide from the milieu, via ACE2, could promote disease regression. Therefore, it was proposed that medications aimed at increasing ACE2 expression would reduce, not increase, COVID-19 pathologies. In this regard, we propose that theories based on no evidence, or 'theoretical opinions', should not be treated with the same esteem as theories based on evidence. Such theoretical opinions would render the scientific community akin to following 'educated conspiracy theories', and fall into the logical fallacy 'appeal to authority'.

We published a paper on DIZE [8] showing its effect at increasing ACE2 activity. We have also noted that DIZE increases ACE2 protein in blood vessels (manuscript submitted) but whether or not DIZE can directly bind to ACE2 is currently unknown. A recent study shows that soluble ACE2 might bind to SARS-CoV-2 virus, thus blocking its ability to bind to cellular ACE2 [23] and ACE2 delivered by an adeno-associated viral vector increased angiotensin (1–7) and reduced angiotensin II levels in a mouse model [24]. Further evidence suggests that ACE2 activation is critical to balance the pro-apoptotic and anti-apoptotic effects by Ang II and Ang (1–7), respectively, in regulating alveolar epithelial cell survival [25]. As 83 % of ACE2-expressing cells are alveolar epithelial cells in healthy lung tissue of adult donors, the suggestion to inhibit ACE2 activity in treating COVID-19 might lead to worsened outcomes. Finally, a recent pre-print suggested that DIZE may have the potential to prevent the production of cytokine storm (an inflammatory response) produced in patients with SARS-CoV2 [26]. Although anti-virals are being developed and tested [27,28], we propose that ACE2 co-therapy could be used to prevent SARS-CoV-2 complications.

Contributors

Tawar Qaradakhi contributed data and contributed to the writing and revision of this editorial.

Laura Gadanec contributed data and contributed to the writing and revision of this editorial.

John Matsoukas contributed to the writing and revision of this editorial.

Vasso Apostolopoulos conceptualized the editorial and contributed to the writing and revision of this editorial.

Anthony Zulli conceptualized the editorial and contributed to the writing and revision of this editorial.

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