Response to four comments on 'Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic?'

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In our recent short report [1], we suggested that angiotensin receptor blocking drug (ARB) prescribing in hypertension may possibly be adverse, because this drug class can increase angiotensin-converting enzyme-2 (ACE2) expression, this protein being the molecular latch for SARS-CoV-2 virus entry to cells in COVID-19 infections. We also suggested, more generally, that *reducing ACE2 expression could be a therapeutic principle for COVID-19 control*. We now welcome medical letters from four correspondents. One, Dr Ekan Cüre [2] extends the case for possible pharmaceutical hazard in COVID-19, providing evidence that actually some drugs additional to those initially suspected increase membrane ACE2 expression. The other three correspondents, Paolo Verdecchia [3], Francisco Jose Fernandez-Fernandez [4] and Liu and colleagues [5], take a different tack. They suggest that increasing the expression of ACE2 in the lungs can be beneficial in acute respiratory disease syndrome (ARDS), including perhaps that due to COVID-19. Accordingly, pharmacologically inducing increased pulmonary ACE2 with renin-angiotensin system blockers might be helpful in COVID-19.

DOES INCREASED ACE2 EXPRESSION MATTER?

Several types of experiment in animals give credence to the idea that the level of human ACE2 expression may perhaps be important in COVID-19 infection. Knockout mice genetically modified to have no ACE2 are totally resistant to coronavirus infections [6]. There is a converse to this. In two studies, transgenic mice were bred to overexpress human ACE2 [7,8]. These hACE2 transgenic mice demonstrated markedly increased infectivity and lethality when exposed to SARS coronavirus. Despite this type of evidence, it is commonly said that with ARB and ACE-inhibitor dosing in humans, the induction of ACE2 would be insufficient to matter, and anyway, may not be in the lungs. But this criticism can be discounted applying a body of relevant evidence, both experimental and clinical (described in more detail below), deriving from studies in which ARB and ACE-inhibitor dosing has been used to replenish ACE2 in the lungs in lung failure syndromes resulting from influenza virus, acid inhalation and other noxious influences [6,9–11]. Pulmonary ACE2 expression is demonstrably increased by renin-angiotensin block in this context, with strong evidence that it improves survival [6,9–11]. In short, the drugs in question for our hypothesis do induce increased pulmonary ACE2 expression, which has biological benefit in noncoronavirus ARSD. With coronavirus exposure it is plausible to ask, as we do, whether the biological effect of drug-induced pulmonary ACE2 expression may be deleterious, promoting infectivity and lethality.

PHARMACOLOGICAL AND OTHER MECHANISMS WHICH INCREASE ACE2 EXPRESSION

Cüre and Cumhur Cüre [2] importantly extend the spectre of possible pharmaceutical hazard in COVID-19 by providing evidence that statins, specifically rosuvastatin [12] and some antidiabetic drugs, possibly sodium-glucose transporter protein 2 (SGLT2) inhibitors [13] and certainly glucagon-like peptide-1 receptor (GLP-1) agonists [14] increase membrane ACE2 expression. In our hypothesis [1], we were circumscribed and specific, focusing on ARBs and hypertension. Cüre and Cumhur Cüre demonstrate that there may be a need to think more broadly on this matter. He has extended the issue to prescribing of statins and antidiabetics. How these drugs increase ACE2 expression is unclear. For other drugs that influence ACE2 expression, their action on body sodium balance appears to be a common link, with sodium depletion elevating ACE2. ARBs, and less consistently ACE-inhibitors, increase ACE2 expression, and decrease body sodium content [1]. Aldosterone reduces ACE2 expression [15], mineralocorticoid block with spironolactone increases expression [16]. We suggested [1] that elevated plasma angiotensin, a substrate of ACE2, which is elevated by ARBs and accompanies sodium depletion in general, may regulate the expression of the linked enzyme, ACE2. Things turn out not to be as simple as that, which may partly explain why ACE-inhibition, which reduces body sodium, but through a direct action lowers plasma angiotensin, elevates ACE2 less consistently than ARBs. Much as for aldosterone dosing, dietary sodium loading reduces ACE2 expression [17]. This effect of sodium ingestion is relevant to the use of proximal small intestine tissue, accessed by endoscopic biopsy, used in direct studies of human ACE2 [18]. Direct exposure of the duodenum to sodium in a meal could be a confounder.

PULMONARY ACE2 IN SEVERE LUNG INJURY: A POTENTIAL THERAPEUTIC TARGET?

Three of the correspondents, Verdecchio *et al*. [3], Fernandez-Fernandez [4] and Liu and colleagues [5], develop the case, which was first presented in relation to the SARS epidemic [6], which in severe lung injury pulmonary ACE2 is depleted. A special form of this pulmonary ACE2 depletion is seen with coronavirus infections, wherein after the virus binds to the ACE2 protein both are internalized, depleting membrane ACE2 [6]. Depletion of ACE2 is accompanied by accumulation of angiotensin, its substrate, in the lung, with adverse effects. The plasma concentration of angiotensin does rise substantially in severe COVID-19 infections [19]. There is a body of experimental and clinical

evidence, mentioned above, that renin-angiotensin block, by repleting ACE2, is beneficial in noncoronavirus ARDS, caused by influenza viruses, acid inhalation and other noxious influences [6,9–11]. Could this benefit extend to COVID-19 infection? A trial of the ARB losartan in severe COVID-19 infections, based on this line of thinking, has commenced (ClinicalTrials.gov Identifier: NCT04312009).

Such a trial may carry risks of worsening the infection. Benefit from renin-angiotensin system block in acute severe lung disease has not been shown experimentally in coronavirus infections. Augmenting pulmonary ACE2 expression might increase coronavirus uptake and viral load. The classic study of Kuba *et al.* [6] is often misquoted as providing evidence of ARBs and ACE-inhibitors benefiting coronavirus pneumonia. Kuba *et al.* [6] actually administered coronavirus fragments, spike protein, not replicable entire virus. The spike fragments depleted pulmonary ACE2 after binding, aggravating the existing experimental pneumonia, which was improved by pharmacological renin-angiotensin system block. Neither this study, or any others to our knowledge, have demonstrated benefit of renin-angiotensin block in coronavirus infection. The transgenic experimental animals overexpressing hACE2 mentioned above previously were demonstrated to have increased infectivity and lethality with SAR coronavirus [7,8]. Augmentation of virus uptake and replication presumably overwhelmed any specific pulmonary benefits.

TESTING OF THE HYPOTHESIS

Hypotheses are made for testing, and for the hypothesis that some common drugs induce ACE2 overexpression and may be adverse in the COVID-19 pandemic, this testing is urgently required. The most immediate and direct clinical testing should come from interrogating the pandemic databases of China and Lombardy. From these populations, presence of COVID-19 illness, illness severity and death could be matched against, age, preexisting medical diagnoses and drugs prescribed at the onset of COVID-19 illness. The multivariate analyses will not be straightforward. There will be a need to differentiate between any effects of ageing, effects of diseases with increased prevalence accompanying ageing (including hypertension, heart failure and diabetes) and the possible effects of drugs given to treat these diseases.

Why not test the hypothesis of drug-induced COVID-19 risk in experimental animals? Pretreat the animals with ARBs and ACE-inhibitors to induced overexpressed ACE2, then in a blinded experiment expose the animals to the SARS-CoV-2 virus. But that would not work. Most mammals do not have sufficient structural similarity in their ACE2 protein to human ACE2 to be infected by this virus which is now cursing the human mammal.

THE FUTURE

It may be difficult to test this hypothesis. Do we as clinicians just live with it, leaving prescribing unchanged? In hypertension, where there are easier alternative prescribing choices, perhaps we can substitute calcium channel blockers and beta-adrenergic blockers for ARBs, and perhaps ACE-inhibitors, if a decision to change antihypertensive medication is made. For chronic renal disease and heart failure, where ARBs and ACE-inhibitors are specifically protective, changes really cannot be recommended, on the basis of a hypothesis. And 'simply discontinuing medication is strongly discouraged and is not an option' [1].

Some hypotheses in medicine just fade away. They are a product of their time, have no real importance and no enduring legacy. With this hypothesis for many there is plausibility, and for all such 'believers', urgency. What can be the way forward, to prove this hypothesis or refute it?

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Conflicts of interest

There are no conflicts of interest.

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