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Substituting Angiotensin-(1-7) to Prevent Lung Damage in SARS-CoV2 Infection?

Running Title: *Peiró & Moncada; Ang-(1-7) and SARS-CoV2 Infection*

Concepción Peiró, PhD[1,2*] & Salvador Moncada, MD, PhD[3*]

[1]Department of Pharmacology, School of Medicine, Universidad Autónoma de Madrid, Madrid, Spain; [2]Instituto de Investigaciones Sanitarias IdiPAZ, Madrid, Spain; [3]Manchester Cancer Research Centre, The University of Manchester, Manchester, UK

***Addresses for Correspondence:**
Salvador Moncada, MD, PhD, FRS, FMedSci, HonFBPhS
Manchester Cancer Research Centre
The University of Manchester
555 Wilmslow Road, Manchester M20 4GJ
Tel: (+44) 0161 306 0843
Email: salvador.moncada@manchester.ac.uk

Concepción Peiró, PhD
Department of Pharmacology
School of Medicine
Universidad Autónoma de Madrid
Arzobispo Morcillo, 4, 28029 Madrid, Spain
Tel: (+34) 4972409
Fax: +34 4975380
Email: concha.peiro@uam.es

Like SARS coronavirus (SARS-CoV), the new coronavirus (SARS-CoV2), which is causing the epidemic COVID-19, enters human cells by binding to angiotensin-converting enzyme-2 (ACE2) although with a higher affinity[1]. Once attached to ACE2, the viral spike protein is primed by the host serine protease TMPRSS2, which ultimately allows fusion of viral and cellular membranes.

ACE2 is a key protein of the protective branch of the renin-angiotensin system, which converts angiotensin (Ang) II, the main biologically active peptide of the RAS, into its physiological antagonist Ang-(1-7). ACE2 also metabolizes Ang I into Ang-(1-9), which is then converted into Ang-(1-7) by angiotensin-converting enzyme (ACE). Ang-(1-7) opposes the vasoconstrictor, pro-inflammatory, pro-oxidant, pro-proliferative or pro-fibrotic actions exerted by Ang II via AT1 receptors (Figure 1).

The binding of SARS-CoV to the ACE2 catalytic site downregulates the expression of ACE2 leading to increases in Ang II[1]. ACE2 is expressed in many organs, but is particularly abundant in alveolar epithelial cells and lung endothelial cells[2]. This would explain why the lung is especially vulnerable to SARS-CoV2. Indeed, the lethality of SARS-CoV has been shown to be dependent on the loss of key regulatory factors in the lung related to the down-regulation of ACE2[3].

Ang-(1-7) seems to be critical in protecting against lung inflammation and fibrosis. This heptapeptide inhibits alveolar cell apoptosis, attenuates endothelial cell activation and the loss of barrier function and oedema, and limits the synthesis of pro-inflammatory and pro-fibrotic cytokines. This is particularly relevant since both acute lung injury and acute respiratory distress syndrome (ARDS) are accompanied by a cytokine storm and an overwhelming inflammatory response[2]. Indeed, activated endothelial cells are increasingly recognized as main orchestrators of the inflammatory response in ARDS.

Hypertension is a comorbidity that may exacerbate the severity of SARS-CoV2 infection[4]. The underlying mechanisms are not clear, but the antihypertensive drugs such as AT1 receptor blockers (ARB) or ACE inhibitors increase ACE2 expression in animal models and humans. Since ACE2 is the receptor for SARS-CoV2 it has been suggested that in patients treated with those drugs, the increase in the receptor may result in increased infection and therefore exacerbation of disease. Whether these treatments should be abandoned in favour of drugs neutral to ACE2, such as calcium channel blockers, is under discussion[5]. However, there is at present no definitive evidence in humans in favour of this suggestion.

On the other hand, the protective effect of ACE2 over-expression is better understood and has led to the contrasting hypothesis that using ARB might protect against viral induced lung injury. In a model of SARS-CoV infection, the blockade of AT1 receptors revealed itself effective in attenuating pulmonary oedema and severe lung injury[3]. In addition to attenuating the binding of Ang II to its AT1 receptors, the beneficial actions of ARB may be explained by two possible mechanisms: 1) the restored ACE2, normally decreased during the viral infection, helps reducing the concentrations of Ang II[3] and, 2) there is an increased generation of the protective Ang-(1-7).

More clinical and experimental evidence is required to resolve this controversy. Meanwhile, we would like to suggest that during viral infection increasing the Ang-(1-7) concentration might be vital for protecting from endothelial cell activation and lung damage. The use of Ang-(1-7) or one of its mimetics should be considered among other strategies to prevent damage in high risk patients.

Disclosures

None

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Figure Legend

Figure. Diagram representing the main metabolic pathways driven by angiotensin-converting enzyme (ACE) and angiotensin-converting enzyme-2 (ACE2) in the renin-angiotensin system. The pharmacological targets for ACE inhibitors (ACEI) and angiotensin AT1 receptors blockers (ARB) are also shown. Ang, angiotensin.