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Brain, Behavior, and Immunity 87 (2020) 159–160

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Letter to the Editor

Pain: A potential new label of COVID-19

ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
ACE2
Pain

Dear Editor,

According to the World Health Organization (WHO), the global outbreak of novel coronavirus disease 2019 (COVID-19) had infected 3,489,053 people worldwide and caused 241,559 deaths by 5th May 2020. Putting these horrendous numbers aside, pain is raising our concern as a potential complication in survivors of COVID-19.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified as the pathogen of COVID-19. The spike protein on this virus binds the angiotensin-converting enzyme 2 (ACE2) receptor, mediating entry into human cells. The angiotensin-converting enzyme/Angiotensin II/Angiotensin II type 1 receptor (ACE/Ang II/AT1 receptor) and ACE2/angiotensin (1–7)/Mas receptor (ACE2/Ang (1–7)/Mas receptor) pathways are antagonistic parts of the renin-angiotensin system. It has been found that infection with SARS-CoV (now sometimes called SARS-CoV-1), a close relative of SARS-CoV-2, induced a decrease of membrane ACE2 receptors on host cells, resulting in an imbalance of ACE/ACE2 and triggering severe lung injury (Kuba et al., 2005). The above mechanisms may also contribute critically to the pathogenesis of SARS-CoV-2.

However, multiple studies have also detected SARS-CoV-2 in the cerebrospinal fluid of infected patients. Neurological symptoms such as disturbance of consciousness, epilepsy and neuralgia may indicate invasion of SARS-CoV-2 into the central nervous system (Wu et al., 2020). Although the expression of ACE2 receptor in the human nervous system has not been fully identified, ACE2 was detected in neuron and microglia in the spinal dorsal horn of mice (Yamagata et al., 2020). Pre-

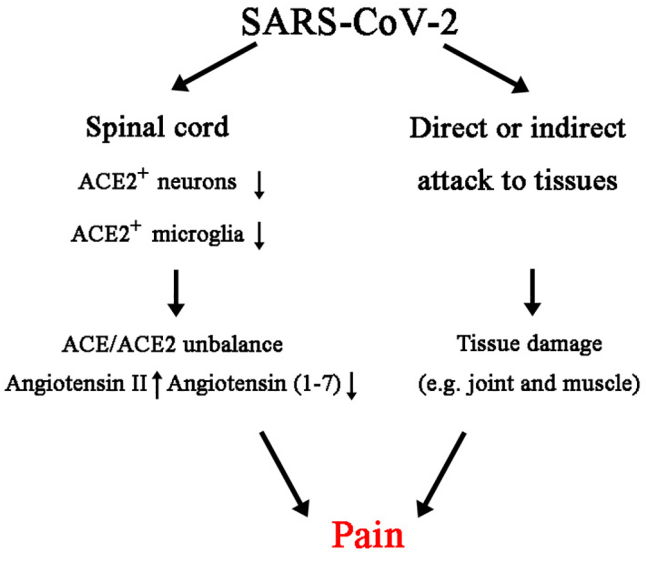

Fig. 1. The potential mechanism of pain induced by SARS-CoV-2 in COVID-19.

https://doi.org/10.1016/j.bbi.2020.05.025
Received 29 April 2020; Received in revised form 5 May 2020; Accepted 6 May 2020
Available online 07 May 2020
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vious studies showed that the ACE/Ang II/AT1 receptor pathway facilitated pain transmission in the spinal dorsal horn, while the ACE2/Ang (1–7)/Mas receptor pathway might alleviate pain through the inhibition of p38 mitogen-activated protein kinase phosphorylation (Nemoto et al., 2013; Yamagata et al., 2020). We suggest that SARS-CoV-2 might infect the ACE2-positive cells in human spinal dorsal horn; the decrease of functional ACE2 then results in the accumulation of Ang II and the decrease of Ang (1–7); consequently, SARS-CoV-2 infection in the spinal cord could induce pain.

In addition to the spinal dorsal horn, SARS-CoV-2 also attacks ACE2-positive cells in other tissues, such as the alimentary canal, kidney and heart, leading to damage to these tissues. Besides the direct attack, SARS-CoV-2 may cause "cytokine storm", involving interleukin (IL)-6, IL-10 and tumor necrosis factor (TNF)-α. This cytokine storm may induce or aggravate damage in various tissues such as joints and muscle, triggering pain-related symptoms (Chen et al., 2020).

Because of the effect of spinal ACE2 on pain sensation and the direct or indirect tissue damage induced by SARS-CoV-2 (Fig. 1), the potential burden of pain induced by COVID-19 cannot be ignored, especially considering the extent of the infected population. The role of ACE2 in pain transmission and pain management for the infected patients will need further investigation in basic and clinical studies, which may provide valuable guidance for public health policy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by grants from National Science Foundation of China #81771205 (Chao Ma), and the CAMS Innovation Fund for Medical Sciences (CIFMS) #2017-I2M-3-008 (Chao Ma).

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