

F. Araya-Quintanilla<sup>a,b,\*</sup>, I. Valdés-Orrero<sup>c</sup>,  
H. Gutiérrez-Espinoza<sup>a,c</sup>

<sup>a</sup> Rehabilitation in Health Research Center, CIREs,  
University of the Americas, Echaurren Street 140, 3rd  
Floor, Santiago, Chile

<sup>b</sup> Faculty of Health, University SEK, Fernando Manterola  
Street 0789, Santiago, Chile

<sup>c</sup> School of Health Sciences, Physiotherapy Department,  
Universidad Gabriela Mistral, Santiago, Chile

\* Corresponding author.  
E-mail address: [fandres.kine@gmail.com](mailto:fandres.kine@gmail.com)  
(F. Araya-Quintanilla).

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## Substance P, proinflammatory cytokines, transient receptor potential vanilloid subtype 1 and COVID-19: a working hypothesis<sup>☆</sup>



## Sustancia P, citocinas proinflamatorias, receptor de potencial transitorio vaniloide tipo 1 y COVID-19: una hipótesis de trabajo

Dear Editor:

The main clinical feature of COVID-19 is respiratory disease of varying severity, ranging from mild upper respiratory tract involvement to severe interstitial pneumonia and acute respiratory distress syndrome, exacerbated by thrombosis of the pulmonary microcirculation.<sup>1</sup> However, it is increasingly apparent that the disease is multisystemic, with the virus entering the central nervous system (CNS) by retrograde neuronal transport via the olfactory nerve and/or enteric nervous system. It has also been suggested that infected leukocytes may cross the blood-brain barrier, transporting the virus to the brain; this would alter the function of brain microvascular endothelial cells, which are known to express angiotensin-converting enzyme 2 (ACE2).<sup>2,3</sup> Neurological signs and symptoms of SARS-CoV-2 infection, associated with expression of the ACE2 receptor in the brain, are thought to be caused by a proinflammatory response in the CNS, promoting microglial activation, the proinflammatory “cytokine storm,” a reduction in levels of CD4 and regulatory T cells, and ultimately the propagation of neuroinflammation.<sup>4,5</sup> However, the precise mechanisms explaining the direct effects of SARS-CoV-2 and the subsequent immune response on the CNS are yet to be fully understood.<sup>6</sup>

The neuroimmune pathway functions bidirectionally, with afferent neurons responding to peripheral immune signals and efferent neurons promoting interaction between the brain and peripheral structures.<sup>7</sup> Transient receptor potential vanilloid subtype 1 (TRPV1) is a nonselective ligand-gated cation channel expressed in neurons, immune

cells, and type C sensory nerve fibres of the airway (upper and lower respiratory tract and lung parenchyma), among other cells; it is highly permeable to Ca<sup>2+</sup> and is reported to be present at increased levels in patients with chronic cough. Mucus hypersecretion and inflammation are also associated with TRPV1 sensitisation.<sup>8,9</sup>

Interaction between the immune, endocrine, and nervous systems involves the participation of neuropeptides, small amino acid molecules that are able to influence immune responses and pain sensitivity through modulation of glial cell activity.<sup>10</sup> The pathophysiological events affecting the severity of COVID-19 have been shown to involve elevated neuronal expression of TRPV1, promoting an increase in the levels of such proinflammatory molecules as substance P and interleukin 6 (IL-6).<sup>11</sup>

Substance P and its selective receptor neurokinin 1 are abundantly expressed in the sensory fibres innervating the respiratory tract and lymphoid organs; such glial cells as microglia and astrocytes, and immune system cells including T cells, monocytes/macrophages, dendritic cells, and eosinophils. The neuropeptide acts as a neurotransmitter, mediating communication between the nervous and immune systems and exacerbating inflammation in such peripheral sites as the lungs.<sup>12</sup> Together, these mechanisms alter the immune functioning of microglia and astrocytes, which are activated in CNS inflammatory processes.<sup>13,14</sup>

Stimulation of TRPV1 by such respiratory pathogens as respiratory syncytial virus promotes the release of numerous molecules including substance P and IL-6.<sup>9,11</sup> Elevated levels of these molecules have been detected in patients with COVID-19, and seem to be associated with more severe disease.<sup>11</sup> All this evidence suggests the activation of a positive feedback mechanism in which increased levels of a harmful stimulus activates TRPV1, leading to greater release of substance P and proinflammatory cytokines, which would result in disease exacerbation in patients infected with SARS-CoV-2.

Despite the massive expansion of our understanding of COVID-19, no study has clarified the association between the neuroimmune function of inflammatory cytokines, neuropeptides, and the role of TRPV1 in the disease. Therefore, we may ask ourselves whether the cytokine storm is directly related with the increase in substance P levels in inflammatory processes in patients with SARS-CoV-2.

We should underscore that the secretion of substance P and cytokines involved in the cytokine storm involves the participation of TRPV1 ion channels, which can be activated by such external insults as viral infection. Therefore, it is reasonable to suppose that neuroimmune communication is established in order to protect the individual; ironically, this

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mechanism would actually increase the severity of COVID-19.

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## References

- Romagnoli S, Peris A, De Gaudio A, Geppetti P. SARS-CoV-2 and COVID-19: from the bench to the bedside. *Physiol Rev*. 2020;100:1455–66, <http://dx.doi.org/10.1152/physrev.00020.2020>.
- Holmes EA, O'Connor RC, Perry VH, Tracey I, Wessely S, Arseneault L, et al. Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science. *Lancet Psychiatry*. 2020;7:547–60, [http://dx.doi.org/10.1016/S2215-0366\(20\)30168-1](http://dx.doi.org/10.1016/S2215-0366(20)30168-1).
- Raony Í, de Figueiredo CS, Pandolfo P, Giestal-de-Araujo E, Oliveira-Silva Bomfim P, Savino W. Psycho-neuroendocrine-immune interactions in COVID-19: potential impacts on mental health. *Front Immunol*. 2020;11:1170, <http://dx.doi.org/10.3389/fimmu.2020.01170>.
- Chen Z, Zhong D, Li G. The role of microglia in viral encephalitis: a review. *J Neuroinflammation*. 2019;16:76, <http://dx.doi.org/10.1186/s12974-019-1443-2>.
- Stearo L, Steardo L Jr, Zorec R, Verkhatsky A. Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. *Acta Physiol (Oxf)*. 2020;229:e13473, <http://dx.doi.org/10.1111/apha.13473>.
- Troyer EA, Kohn JN, Hong S. Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. *Brain Behav Immun*. 2020;87:34–9, <http://dx.doi.org/10.1016/j.bbi.2020.04.027>.
- DosSantos MF, Devalle S, Aran V, Capra D, Roque NR, Coelho-Aguiar JM, et al. Niemeyer Soares Filho P, Moura-Neto V. Neuromechanisms of SARS-CoV-2: a Review. *Front Neuroanat*. 2020;14:37, <http://dx.doi.org/10.3389/fnana.2020.00037>.
- Zhang X, Ye L, Huang Y, Ding X, Wang L. The potential role of TRPV1 in pulmonary hypertension: angel or demon? *Channels (Austin)*. 2019;13:235–46, <http://dx.doi.org/10.1080/19336950.2019.1631106>.
- Omar S, Clarke R, Abdullah H, Brady C, Corry J, Winter H, et al. Respiratory virus infection up-regulates TRPV1, TRPA1 and ASIC3 receptors on airway cells. *PLoS One*. 2017;12:e0171681, <http://dx.doi.org/10.1371/journal.pone.0171681>.
- Carniglia L, Ramírez D, Durand D, Saba J, Turati J, Caruso C, et al. Neuropeptides and microglial activation in inflammation, pain, and neurodegenerative diseases. *Mediators Inflamm*. 2017;2017:5048616, <http://dx.doi.org/10.1155/2017/5048616>.
- Nahama A, Ramachandran R, Cisternas AF, Ji H. The role of afferent pulmonary innervation in poor prognosis of acute respiratory distress syndrome in COVID-19 patients and proposed use of resiniferatoxin (RTX) to improve patient outcomes in advanced disease state: a review. *Med Drug Discov*. 2020;5:100033, <http://dx.doi.org/10.1016/j.medidd.2020.100033>.
- Suvas S. Role of Substance P Neuropeptide in inflammation, wound healing, and tissue homeostasis. *J Immunol*. 2017;199:1543–52, <http://dx.doi.org/10.4049/jimmunol.1601751>.
- Johnson MB, Young AD, Marriott I. The therapeutic potential of targeting substance P/NK-1R interactions in inflammatory CNS disorders. *Front Cell Neurosci*. 2017;10:296, <http://dx.doi.org/10.3389/fncel.2016.00296>.
- Kaczyńska K, Zając D, Wojciechowski P, Kogut E, Szereda-Przestaszewska M. Neuropeptides and breathing in health and disease. *Pulm Pharmacol Ther*. 2018;48:217–24, <http://dx.doi.org/10.1016/j.pupt.2017.12.001>.

E.E. Aguirre-Siancas\*, E. Colona-Vallejos, E. Ruiz-Ramirez, M. Becerra-Bravo, L. Alzamora-Gonzales

*Universidad Nacional Mayor de San Marcos, Lima, Peru*

\* Corresponding author.

*E-mail address:* [eaguirres@unsm.edu.pe](mailto:eaguirres@unsm.edu.pe)  
(E.E. Aguirre-Siancas).

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## Isolated syncope as a form of presentation of COVID-19 infection<sup>☆</sup>

### Síncope aislado como forma de presentación de infección por COVID-19

*Dear Editor:*

SARS-CoV-2 infection has become a severe public health problem; presentation of the infection ranges from mild



or even asymptomatic forms to severe pneumonia or acute respiratory distress syndrome, which can be fatal.<sup>1–6</sup> Early identification of the infection is essential to ensuring proper isolation and clinical monitoring of these patients and their households. Most patients do present symptoms, with the most frequent being fever (72.3% of cases), respiratory symptoms, digestive symptoms, and neurological symptoms.<sup>6</sup> We describe an exceptional case of a patient without known cardiac disease who presented syncope as the only manifestation of SARS-CoV-2 infection.

The patient was a 78-year-old man, a former smoker, with history of arterial hypertension, dyslipidaemia, hyperuricaemia, chronic bronchitis, and pulmonary fibrosis due to asbestos exposure at work. He had no known heart conditions and denied having presented such symptoms as dyspnoea, angina, or palpitations. The patient was receiving long-term treatment with atorvastatin, enalapril, omepra-

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