

Pain relief caused by SARS-CoV-2 infection may help explain COVID-19 spread

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Doctoral student Lisa Boinon prepares buffers while Dr. Rajesh Khanna looks on. Credit: University of Arizona Health Sciences, Kris Hanning

SARS-CoV-2, the virus that causes COVID-19, can relieve pain, according to a new study by University of Arizona Health Sciences

researchers.

The finding may explain why nearly half of people who get COVID-19 experience few or no symptoms, even though they are able to spread the disease, according to the study's corresponding author Rajesh Khanna, Ph.D., a professor in the College of Medicine—Tucson's Department of Pharmacology.

"It made a lot of sense to me that perhaps the reason for the unrelenting spread of COVID-19 is that in the early stages, you're walking around all fine as if nothing is wrong because your pain has been suppressed," said Dr. Khanna. "You have the virus, but you don't feel bad because your pain is gone. If we can prove that this pain relief is what is causing COVID-19 to spread further, that's of enormous value."

The paper, "SARS-CoV-2 Spike protein co-opts VEGF-A/Neuropilin-1 receptor signaling to induce analgesia," will be published in *PAIN*, the journal of the International Association for the Study of Pain.

The U.S. Centers for Disease Control and Prevention released updated data Sept. 10 estimating 50% of COVID-19 transmission occurs prior to the onset of symptoms and 40% of COVID-19 infections are asymptomatic.

"This research raises the possibility that pain, as an early symptom of COVID-19, may be reduced by the SARS-CoV-2 spike protein as it silences the body's pain signaling pathways," said UArizona Health Sciences Senior Vice President Michael D. Dake, MD. "University of Arizona Health Sciences researchers at the Comprehensive Pain and Addiction Center are leveraging this unique finding to explore a novel class of therapeutics for pain as we continue to seek new ways to address the opioid epidemic."

Viruses infect host cells through protein receptors on cell membranes. Early in the pandemic, scientists established that the SARS-CoV-2 spike protein uses the angiotensin-converting enzyme 2 (ACE2) receptor to enter the body. But in June, two papers posted on the preprint server bioRxiv pointed to neuropilin-1 as a second receptor for SARS-CoV-2.

"That caught our eye because for the last 15 years my lab has been studying a complex of proteins and pathways that relate to pain processing that are downstream of neuropilin," said Dr. Khanna, who is affiliated with the UArizona Health Sciences Comprehensive Pain and Addiction Center and is a member of the UArizona BIO5 Institute. "So we stepped back and realized this could mean that maybe the spike protein is involved in some sort of pain processing."

Many biological pathways signal the body to feel pain. One is through a protein named vascular endothelial growth factor-A (VEGF-A), which plays an essential role in blood vessel growth but also has been linked to diseases such as cancer, rheumatoid arthritis and, most recently, COVID-19.

Like a key in a lock, when VEGF-A binds to the receptor neuropilin, it initiates a cascade of events resulting in the hyperexcitability of neurons, which leads to pain. Dr. Khanna and his research team found that the SARS-CoV-2 spike protein binds to neuropilin in exactly the same location as VEGF-A.

With that knowledge, they performed a series of experiments in the laboratory and in rodent models to test their hypothesis that the SARS-CoV-2 spike protein acts on the VEGF-A/neuropilin pain pathway. They used VEGF-A as a trigger to induce neuron excitability, which creates pain, then added the SARS-CoV-2 spike protein.

"The spike protein completely reversed the VEGF-induced pain

signaling," Dr. Khanna said. "It didn't matter if we used very high doses of spike or extremely low doses—it reversed the pain completely."

Dr. Khanna is teaming up with UArizona Health Sciences immunologists and virologists to continue research into the role of neuropilin in the spread of COVID-19.

In his lab, he will be examining neuropilin as a new target for non-opioid pain relief. During the study, Dr. Khanna tested existing small molecule neuropilin inhibitors developed to suppress tumor growth in certain cancers and found they provided the same [pain](#) relief as the SARS-CoV-2 spike [protein](#) when binding to neuropilin.

"We are moving forward with designing small molecules against neuropilin, particularly natural compounds, that could be important for [pain relief](#)," Dr. Khanna said. "We have a pandemic, and we have an opioid epidemic. They're colliding. Our findings have massive implications for both. SARS-CoV-2 is teaching us about viral spread, but COVID-19 has us also looking at neuropilin as a new non-opioid method to fight the opioid epidemic."

More information: Aubin Moutal et al. SARS-CoV-2 Spike protein co-opts VEGF-A/Neuropilin-1 receptor signaling to induce analgesia, *Pain* (2020). [DOI: 10.1097/j.pain.0000000000002097](https://doi.org/10.1097/j.pain.0000000000002097)

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