Study finds potential mechanism for “brain fog” in Long COVID

Bill Shaw
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A new study published in the journal *Cell* has uncovered a potential biological mechanism for so-called “brain fog” in Long COVID. Brain fog emerged as one of the first well-described symptoms of Long COVID in the early phases of the pandemic. Brain fog is not one particular symptom, but rather is an array of one or more symptoms that can include difficulty concentrating, memory loss, confusion, thinking more slowly than usual, “fuzzy thinking,” and feeling dazed.

The researchers found that the levels of a compound called “serotonin” in the blood were lower in Long COVID patients than in patients who had recovered from SARS-CoV-2 infection without long-term effects. Serotonin is a neurotransmitter, which is a molecule released by neurons to communicate with other neurons. Other neurotransmitters include epinephrine, dopamine, and acetylcholine.

The researchers studied mice to determine that a drop in blood serotonin levels reduces the activity of neurons whose function is sensory input. Specifically, sensory neurons in the vagus nerve were significantly impacted by the low levels of serotonin. These neurons primarily exist in core body organs including the heart, lungs, and gastrointestinal tract, providing sensory information from these visceral organs to the brain.

This result is surprising, as the researchers themselves hypothesized that the well-known role of serotonin in the brain would be directly connected to brain fog. The reason is that in the central nervous system, serotonin plays a crucial role in sleep, memory, pain signaling, learning, sexual activity, biological rhythms, and many other functions.

However, the researchers found that brain levels of serotonin were normal in mice infected with SARS-CoV-2. Animal models of disease are frequently used by researchers to study aspects of disease that are difficult or impossible to study in humans. In this case, the researchers infected mice with SARS-CoV-2 and employed well-known tests of memory in mice. They could then sacrifice these mice to obtain tissue samples from their brains, vagus nerves, and other organs to measure levels of serotonin and perform additional relevant tests.

Although the peripheral effects of reduced serotonin on brain fog were surprising, there is a known direct connection. Increased stimulation of sensory fibers in the vagus nerve activates a brain region called the hippocampus, which is crucial to memory formation. A study in rats in 2018 found that “chemically cutting” vagus-nerve-mediated input from the gastrointestinal tract impaired the formation of episodic and spatial memories known to require the hippocampus. That study also identified for the first time the neural pathway connections from the vagus nerve all the way to the hippocampus.

The researchers determined the association between low sensory nerve activity and reduced performance on memory-related tasks by administering drugs to mice that directly increased the activity of the sensory nerves. First, the restoration of serotonin levels restored memory. Second, the administration of capsaicin restored memory as well. Capsaicin was previously known to be a direct and strong simulator of sensory neurons.

The researchers also identified the biological pathway by which serotonin activates sensory neurons. First, they identified high levels of expression of particular serotonin receptors called “5-HT3 receptors” on the cellular membranes of these cells. Second, they administered another compound called “*meta*-Chlorophenylbiguanide” or *m*-CPBG to the mice. This compound is known to bind to

5-HT3 receptors with the same effects as serotonin. Administration of m-CPBG also restored memory-based performance in the mice.

The study found three causes of low serotonin levels, all of which are related to ongoing viral replication in body tissues. Specifically, persistent SARS-CoV-2 replication in the body leads to reduced absorption of serotonin precursors from the diet, lowered platelet counts, and increased activity of enzymes that break down serotonin. The significance of the lowered platelet counts is that platelets are the major component of blood that carries serotonin throughout the body.

A key strength of the study is that the researchers extensively ruled out other explanations for reduced serotonin. For example, they found that activity of the enzymes that convert tryptophan to serotonin was not impacted. They also found that the genes involved in tryptophan absorption of the gut were downregulated in the presence of type 1 interferon, which is known to be elevated in the presence of ongoing viral replication. Furthermore, they verified that genetic alterations expected to block interferon-induced downregulation did indeed prevent it.

Another strength of the study is that it examined in an agnostic manner thousands of so-called “metabolites” in acute SARS-CoV-2 and Long COVID patients. The only metabolite consistently reduced in both patient populations, and that was highly correlated with symptoms, was serotonin. The subsequent detailed elucidation of the biological mechanism of reduced serotonin, as well as ruling out of alternative biological mechanisms, provides high confidence in the results.

Another key finding of the study is that the effect is not specific to SARS-CoV-2. The researchers found reduced serotonin levels in both human and mouse subjects with other viral infections.

The limitations of the study are that although mice are susceptible to SARS-CoV-2 infection, there is no mouse model of Long COVID itself. Thus, whether the observed reduction in mouse performance in memory-based tasks correlates with human Long COVID symptoms is unknown. Also, the effects of low serotonin levels were quite variable among Long COVID patients. The study also suffered from relatively small sample size, with 58 patients from one United States hospital.

Nevertheless, the study is a major milestone in understanding the pathology of acute SARS-CoV-2 infection and viral infections generally, identifying reduced serotonin levels as a common factor. The study also provides important future directions for Long COVID research that did not exist previously. Furthermore, it represents an impressive achievement in enhancing our understanding of the interaction among viral infection, the peripheral nervous system, and the central nervous system.

Finally, the study adds to the evidence that ruling class indifference to widespread viral infections across the globe will continue to needlessly cause human suffering. The lesson for the working class is that until the global economy is based on human need and not profit, viral infections will be permitted to spread, causing massive morbidity and mortality.