The Washington Post
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BRAIN MATTERS

# How inflammation in the body may explain depression in the brain

Inflammation is a pathway to depression — and a potential avenue for treatment, research suggests

By Richard Sima

February 23, 2023 at 12:04 p.m. EST

(George Wylesol for The Washington Post)

One in five Americans will experience major depressive disorder in their lifetime, and many will not find relief from current therapies. But now researchers have identified an unexpected source of the problem: inflammation.

Inflammation in the body may be triggering or exacerbating depression in the brains of some patients. And clinical trial data suggests that targeting and treating the inflammation may be a way to provide more-precise care.

The findings have the potential to revolutionize medical care for depression, an often intractable illness that doesn't always respond to conventional drug treatments. While current drug treatments target certain neurotransmitters, the new research suggests that in some patients, depressive behaviors may be fueled by the inflammatory process.

It appears that inflammatory agents in the blood can break down the barrier between the body and the brain, causing neuroinflammation and altering key neural circuits, researchers say. In people at risk for depression, inflammation may be a trigger for the disorder.

Research suggests that only a subset of depressed patients — roughly 30 percent — have elevated inflammation, which is also associated with poor responses to antidepressants. This inflammatory subgroup may be a key to parsing out differences in underlying mechanisms for depression and personalizing treatment.

"Activation of these inflammatory pathways in the body and brain is one of the ways through which depressive symptoms can be produced," said Charles Raison, a professor of human psychology, human ecology and psychiatry at the University of Wisconsin at Madison.

**The challenge of treating depression**

Depression is itself a risk factor for several other diseases and disorders, including obesity, diabetes, cardiovascular disease, chronic respiratory disorders and arthritis. Depression is the major cause of suicide, which is a leading cause of death in the United States.

One person's depression is not necessarily the same as another's. "It's not that depression is sort of this generic disorder that is the same for all people," said Andrew Miller, a professor of psychiatry and behavioral sciences at the Emory University School of Medicine. "It's quite different depending on who it is and what they're experiencing."

From the nine symptom criteria — depressed mood, diminished pleasure, weight change, sleep change, lethargy, feelings of worthlessness, attention problems, psychomotor disturbance or suicidal ideation — there are 227 possible combinations for being diagnosed with major depressive disorder,

though some combinations are more common than others. For many people, this makes it difficult to find an effective treatment.

Antidepressants, a standard treatment for most depressive disorders, are designed to modulate the transmission of certain neurotransmitters — serotonin, dopamine and norepinephrine — but only about 30 percent of patients go into remission following treatments. While many others may find partial relief from antidepressants along with behavioral therapy, an estimated 50 percent of depressed patients are inadequately treated and 30 percent are resistant to current treatments.

Newer treatments such as ketamine are helping some people, but have their own problems and side effects.

**The inflamed body and the depressed brain**

Inflammation is the response produced by the immune system to protect the body from pathogens, injuries and toxins. But chronic inflammation, which can be caused by stress, poor diet, an unhealthy lifestyle or autoimmune diseases, can damage cells and organs and increase risk for a number of health problems.

A number of studies show that depressed patients tend to have increased inflammation compared with non-depressed subjects, including more inflammatory cytokines and C-reactive protein — which is produced by the liver in response to inflammation — circulating in the blood. Patients with autoimmune diseases have inordinately high rates of depression. And postmortem brain samples from people who died by suicide showed more activation of the brain's immune cells, which release inflammatory agents.

Crucially, pro-inflammatory drugs can induce people to become depressed, which suggests a causative link. In one seminal studypublished in the New England Journal of Medicine, Miller and his colleagues conducted a double-blind study of 40 cancer patients undergoing treatment with interferon-alpha, an inflammatory cytokine.

Though none of the patients had depression to begin with, the inflammatory agent had a striking effect: Many became depressed, a finding that has been consistently replicated.

“The patients recognize pretty much immediately that, ‘Hey, you gave me something, and now I feel this way. I don’t know why I feel this way,’” Miller said.

**Inflammation changes brain circuits and behavior**

From an evolutionary standpoint, inflammation may be a way for the immune system to communicate with the brain, Miller said. When animals were wounded or fighting off an infection, the brain and immune system would work in concert to shut down the animal’s activities to allow for quicker recovery.


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But for humans today, living in more sanitary environments and with relatively new sources of inflammation — unhealthy foods, sedentary lifestyles — this immune response may be less adaptive because the inflammation is less likely the result of an infection or wound.

“Now we live in an environment where we’re not terribly physically active, we eat a ton of carbs, we’re overweight by and large, and it’s killing us,” Miller said. “The inflammation is killing us. And one of the ways that it kills us is by affecting the brain.”

But how inflammation influences depression is complex. Inflammation may be increasing anhedonia, or the depressive symptom of reduced pleasure. It may also play a role in causing psychomotor slowing, or the slowing down of thought and movement.

People receiving pro-inflammatory agents such as interferon-alpha had blunted responses in brain areas associated with reward, such as the ventral striatum. Inflammation also seems to decrease the release of dopamine, a neurotransmitter implicated in reward and movement.

At the same time, inflammation reduces the functional connectionsbetween the ventral striatum and the prefrontal cortex, which are important parts of the brain's reward circuitry.

**A leaky blood-brain barrier**

Prolonged, elevated inflammation can lead to a leakier blood-brain barrier, which normally protects the delicate brain from potentially harmful molecules in the blood. But when chronic inflammation is present, immune cells in the blood glue themselves to the barrier blood vessels, where they constantly release inflammatory molecules. These may activate the brain's specialized immune cells on the other side of the barrier, called microglia, to release inflammatory agents of their own and cause neuroinflammation.

"This will fragilize the blood-brain barrier," said Caroline Ménard, an assistant professor of psychiatry and neuroscience at Université Laval and CERVO Brain Research. "So eventually, you will have some tiny holes in the blood-brain barrier of the brain. And this will allow inflammation to pass from the blood into the brain, and this will eventually change the neurons and all the cells that create the behavior and who we are."

Ménard and her colleagues discovered, in one mouse study, that chronic stress and inflammation caused the blood-brain barrier to get leaky in specific areas involved in depression, such as the nucleus accumbens, a key structure in the ventral striatum. When the researchers examined the nucleus accumbens in postmortem brain tissue of depressed male patients in a 2020 study, they found similar molecular changes in the blood-brain barrier.

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Interestingly, there are sex differences in how inflammation affects the blood-brain barrier. When the researchers ran similar experiments in female mice in a 2022 study, they found that chronic social stress caused the blood-brain barrier to be leaky in a different part of the brain — the prefrontal cortex, a mood-related hub. Postmortem brain tissue of depressed women exhibited similar vascular alterations in the blood-brain barrier near the prefrontal cortex.

These results suggest one possible mechanism for how inflammation, a whole-body process, could affect certain depression-relevant parts of the brain, such as the ventral striatum and prefrontal cortex, more than others: A leaky blood-brain barrier could cause neuroinflammatory changes to nearby neurons in the reward circuit.

The coordinated involvement of the immune, vascular and nervous systems also underscores that depression is a whole-body problem that requires a whole-body approach to solving it.

"I think we need to think outside the box, which is the brain and the neurons," Ménard said. "When you're stressed, you feel it all over your body, you don't feel it only in your brain."

**Can treating inflammation treat depression?**

If inflammation can induce or exacerbate depression and its symptoms, then reducing inflammation could provide relief.

Even if inflammation is a disease modifier rather than the cause of the problem, "you have to take care of it in order for you to be able to get your therapeutics working to restore your circuitry and what's happening in the mind," said Eleonore Beurel, a professor of psychiatry and behavioral sciences at the University of Miami Miller School of Medicine.

Anti-inflammatory drugs, used alone or in conjunction with a standard antidepressant, may help some depressed patients. A 2019 meta-analysis encompassing almost 10,000 patients from 36 randomized clinical trials found that different anti-inflammatory agents, including NSAIDs, cytokine inhibitors and statins, could improve depressive symptoms.

But some recent large clinical trials testing anti-inflammatory drugs have not found any noticeable impact on depressed patients.

Part of the issue is that anti-inflammatory treatments should target only patients with elevated inflammation — and not be used as a one-size-fits-all approach, because depression is so heterogeneous. Most clinical trials are not designed to compare inflammation levels of patients, but analyses run post-hoc suggest that anti-inflammatories have the largest effect on depressed patients with inflammation, Miller said. For example, one early randomized controlled trial conducted by Miller and Raison found that giving a cytokine inhibitor to treatment-resistant depression patients helped only those with elevated inflammation.

Future research trials need to consider the heterogeneity of the patients and their different flavors of depression as well as their inflammatory profiles. Making more precise measurements of particular symptoms impacted by inflammation, such as anhedonia and psychosomatic slowing, may also tease apart subtle effects of different treatments.

"We've come to the tipping point," Miller said. "And we know enough at this point to begin to target the immune system and its downstream effects on the brain to treat depression. We are there."

https://www.washingtonpost.com/wellness/2023/02/23/depression-brain-inflammation-treatment/