From: [redacted]
To: jeevacation@gmail.com
Subject: hmm
Date: Mon, 14 Apr 2014 23:46:21 +0000

"If I cut the vagus your body doesn't know it is sick" (or that it should be stressed)
This guy presents sstress as an infection - very interesting
I like the reminder that macrophages can't enter blood brain barrier (duh) so how does it know you are sick?

December 2001 Monitor on Psychology » A new take on psychoneuroimmunology

Cover Story

A new take on psychoneuroimmunology

Research pointing to a circuit linking the immune system and brain connects illness, stress, mood and thought in a whole new way.

By BETH AZAR

December 2001, Vol 32, No. 11

Print version: page 34

Even though doctors have all but rejected the idea that going out in the winter with wet hair causes colds, many mothers still insist it's a recipe for illness. Those moms may soon have data on their side from some new research linking stress and the immune system.

The research indicates that stress--maybe even the stress of being cold--appears to tap into the same immune systemnervous system loop that triggers symptoms of the common cold, according to Steven Maier, PhD, who gave the Neal Miller Lecture at APA's 2001 Annual Convention.

For more than a decade, researchers have known that behavioral and psychological events can influence the immune system. But now new research shows that the immune system sends signals to the brain "that potently alter neural activity and thereby alter everything that flows from neural activity, mainly behavior, thought and mood," said Maier, professor of psychology at the University of Colorado.

"In a real, true sense, stress makes you physically sick," explained Maier. "In addition, many of the changes over time in mood and cognition from day to day are driven by events in the immune system of which we are unaware."

The immune-brain loop

When Maier talks about the immune system, he's not talking about the specific immune response of t-cells, b-cells and antibodies that most psychoneuroimmunologists study. He's more interested in what's called the "nonspecific immune response"--the body's rapid, first-line defense against infection or injury that's initiated an hour or two after infection.

This nonspecific immune response is often called the "sickness" response because it triggers a series of physiological and behavioral changes, including fever, changes in liver metabolism, reduced food and water intake, reduced sexual activity, reduced exploration and increased anxiety. It also activates a classic stress response, releasing stress hormones such as cortisol.

According to Maier, the sickness pattern is an orchestrated attempt to produce energy for fighting infection and to preserve energy through behavior changes. Knowing that signals from the brain--in particular the hypothalamus--trigger these sickness responses, Maier and his colleagues set out to tease apart the molecular machinery at work. The first step was to figure out how the brain knows there's an infection in the first place.

The key lay in molecules called pro-inflammatory cytokines, which include interleukin-1, interleukin-6 and tumor necrosis factor alpha. Immune cells called macrophages, which are the first on the scene of any infection, create these molecules and experiments showed that they act inside the brain to trigger the sickness response.

For example, when Maier and his colleagues inactivate these cytokines or block the receptors in the brain that bind them, animals show no sign of sickness after infection. And if they administer these cytokines to the brain, the animals show all the signs of infection even when no infection exists.

But, Maier and his colleagues found, it's not the cytokines produced in the blood by macrophages that tell the brain you're sick. They're too big to get past the blood-brain barrier. Instead, the message moves from the bloodstream to the vagus nerve, which delivers it to the brain.

"If I cut your vagus," said Maier, who has done such in rats, "your brain doesn't know you're sick."

How does the body translate a blood-borne signal into a neural signal? Sitting along the vagus are pockets of neurotransmitters, called paraganglia, which have on them receptors for interleukin-1--one of the cytokines released by macrophages.

"So, the way this all works is really clever," explained Maier. "Your macrophage chews on a bacteria, it releases interleukin-1 into the neighboring space, the interleukin-1 binds to receptors on the paraganglia, which send neurotransmitters to activate the vagus nerve," which sends a signal to the brain. This signal triggers the brain to make its own interleukin-1 and that sets off the sickness response and sends signals back to the immune system, further activating immune cells.

"We have a complete, bidirectional immune-to-brain circuit," said Maier.

Stress makes you sick

It turns out that stress taps into this very same circuit, but starting in the brain rather than the immune system. Maier and his colleagues find that if they stress animals--by socially isolating them or giving them electrical shock--they see massive increases in interleukin-1 in the hippocampus.

"Stress and infection activate overlapping neural circuits that critically involve interleukin-1 as a mediator," said Maier.

And, not only does stress produce the expected stress response, it also produces exactly the same behavioral changes--including decreased food and water intake and decreased exploration--and physiological changes, including fever, increased white blood cell count and activated macrophages seen in the "sickness response."

"These animals are physically sick after stress," said Maier. "You see everything you see with infection."

The implications of this shared neural loop are that stress and infection sensitize the body's reaction to the other. In other words, an infection primes the circuit so that it has an exaggerated response to later stress and vice versa.

"How you react to a stressor or an infectious agent depends critically on events of the other type in the past," said Maier. And, he added, the effect isn't short-lived. He's measured it out to 10 days.

And so it appears that stress enhances immunity--at least the nonspecific, first-line immunity, said Maier, which makes some evolutionary sense. If we're under stress-- about to be attacked by a wild animal, for example--we would want to prime our first-line immune response to be ready in case of injury.

"Stress is another form of infection," he said. "And the consequences of stress are mediated by the activation of circuits that actually evolved to defend against infection."

Depression and cognition

Understanding this dual-function circuitry may help psychologists better understand depression, said Maier. In fact, depressed mood produces all the same behavior changes as both the sickness and stress responses--changes that conserve energy and keep people out of harm's way. In some sense, it could be thought of as a highly efficient circuit for triggering these adaptive changes.

Evidence for connecting depression with the sickness/stress circuitry comes from studies in animals and humans. For example, studies of patients receiving interleukin-1 to fight cancer found that they developed severe depression and, vice versa, people with depression have elevated cytokine levels.

Clinical studies have also associated cytokines with cognitive impairments, said Maier, which led him to his most recent work attempting to link changes in the immune system with day-to-day variability in cognitive function.

Preliminary work finds that he can disrupt learning and memory in rats by injecting bacteria into rats' digestive tracts or by injecting interleukin-1 into their hippocampus. He and his colleagues are now trying to work out the molecular mechanisms that cause the disruptions in learning and memory.

"This is a really exciting time for psychoneuroimmunology," concluded Maier. "We're finding that products of the immune system alter neural activity and everything else that flows from neural activity. It's not very unusual anymore to think of hormones as regulating neural function, and I believe that in another few years it will be no less unusual to think of immune products regulating neural function."

Beth Azar is a writer in Portland, Ore.