New Clues to the Neurobiology of Depression

To fully understand the neurobiology of major depression, mental health professionals must adopt a perspective that considers interactions between the brain, the outside world, and the body, including the immune system.

“Don’t overestimate the brain,” said Charles Raison, MD, Psych Congress Steering Committee member and Associate Professor of Psychiatry at the University of Arizona. He discussed the mind-body interface in a pre-conference presentation at the 27th Annual U.S. Psychiatric and Mental Health Congress.

According to Dr. Raison, the brain may appear separate from the immune system, but the two systems actually have a bidirectional relationship that profoundly impacts psychiatric illness.

HPA Axis

For example, the HPA axis (hypothalamic–pituitary–adrenal axis) starts in the brain yet affects the entire body. The end product of the HPA axis is the production of cortisol, the body’s primary stress hormone.

Cortisol serves a dual purpose in the body, functioning as both the primary stress hormone and as the primary anti-stress hormone.

“None of us would design a machine this way, a car with one pedal that’s the gas and the brake, but that’s really how nature built the body,” said Dr. Raison. He added, “My bias is that it is cortisol’s anti-stress activities that seem to be most impaired in depression. It seems to me that depression can be seen as a condition of insufficient cortisol signaling, even when there’s too much cortisol in the blood.”

Unlike neurotransmitters which tend to signal via membrane-bound receptors, cortisol’s primary biological effects result from its binding to receptors that reside inside of cells in the cytoplasm. Once these receptors are bound, the cortisol/receptor complex moves to the cellular nucleus where it binds with DNA promoter sites and changes how proteins are eventually produced.

Cortisol has two main types of receptors, mineralocorticoid receptors that come into play when cortisol levels are low, and glucocorticoid receptors that have less sensitivity to cortisol. As cortisol levels rise, the mineralocorticoid receptors saturate, leaving the glucocorticoid receptors to take center stage. “It’s because of this that glucocorticoid receptors are the primary transducers of stress effects of cortisol, and it’s been glucocorticoid receptors that have been most extensively studied in psychiatry,” said Dr. Raison.

Researchers have known for years that people with depression have elevated cortisol, but the higher levels of cortisol may not be the primary abnormality. Evidence shows that the sensitivity of the glucocorticoid receptor is decreased in people with depression, meaning that the HPA axis is unable to turn itself off and therefore releases more and more cortisol.

Stress System Abnormalities

As important as the HPA axis is, the brain and the body have other important ways of communicating about stress and danger. Dr. Raison’s research group and others have found that many of the symptoms of depression are remarkably similar to those of sickness, even to the extent of developing a fever. In fact, research suggests that inflammatory processes are a pathway through which the body can induce depression in the brain.

This phenomenon is illustrated in non-depressed patients who undergo cancer or hepatitis C treatment with the drug interferon-alpha, which is known to cause inflammation. Research shows that an average of 50% of these patients will develop clinically significant depressive symptoms over a three-month treatment period. Interestingly, if the patients are pre-treated with selective serotonin reuptake inhibitor antidepressants, the risk for developing depression during interferon-alpha treatment is significantly reduced.

“This is just part of the evidence that you can take people who are not depressed, put them under chronic inflammation, and almost all of them develop depressive symptoms and many will develop major depression. The emotional changes that result from chronic inflammation look like depression, smell like depression, and respond to antidepressants like depression,” said Dr. Raison.

In day-to-day life, the inflammatory process is often provoked by psychosocial stress. Dr. Raison and others have hypothesized that this response is a relic of pre-modern times during which the brain and body recognized that psychological distress was an early warning sign of impending infection as a result of wounding. With infection imminent, the body readied itself by ramping up the inflammatory response.

Although stress seems to increase inflammation in most people, individuals who have a history of early life trauma, abuse, or neglect are especially susceptible. Many animal studies suggest that early life adversity programs the body to respond to even

minor threats with hyperactivity of inflammatory systems, which may in turn explain why early life trauma and neglect are such powerful predictors of developing inflammation-related illnesses in adulthood.

“In animals and humans there’s evidence that undergoing trauma and neglect early in life programs the body to run danger pathways and run hot, an inflammatory system that shoots first and asks questions later.” He added, “The royal road to inflammation is early life adversity.”

Living in a Microbial World

Yet the interplay of inflammation and depression extends beyond psychosocial stress and beyond even the cells in our body to the vast bacteria and virus-laden world we inhabit. As human beings, we are greatly outnumbered by bacteria in our own bodies. Even at the cellular level—only 1 in 10 cells in our body is mammalian, the rest are bacterial.

“Bacteria are everywhere the body meets the world,” said Dr. Raison. “The psychoneuroimmunological perspective suggests you’re not an individual, you’re a community.”

During evolutionary times, humans and other primates were in direct contact with bacteria and other organisms that the immune system learned to tolerate. Eventually the immune system counted on the organisms as a way of teaching tolerance.

However, as hygiene and modernity progressed, we lost contact with these beneficial microorganisms, as well as with many of the deadly ones that led to infection and death.

“Depression in the modern world may be due at least in part to the fact that we’ve been overly successful, overly hostile to the microbial world,” said Dr. Raison. “We don’t want to go back to dying of infection, but exposing ourselves in childhood to immunotolerant organisms may promote physical and mental health.”

For mental health professionals, better understanding and treating depression means going beyond the brain alone. “A mind-body perspective suggests that we really need to be looking at the much larger sphere of interactions between the brain, the body, and the larger world if we’re going to fully understand the neurobiology of major depression,” Dr. Raison concluded.

—Lauren LeBano

Reference

1. Raison C. [pre-conference presentation]. July 15, 2014. http://www.psychcongress.com/neurobiology. Accessed August 20, 2014.