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New study explains how stress can boost immune system

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A study spearheaded by a Stanford University School of Medicine scientist has tracked the trajectories of key immune cells in response to short-term stress and traced, in great detail, how hormones triggered by such stress enhance immune readiness. The study, conducted in rats, adds weight to evidence that immune responsiveness is heightened, rather than suppressed as many believe, by the so-called "fight-or-flight" response.

The study's findings provide a thorough overview of how a triad of stress hormones affects the main cell subpopulations of the immune system. They also offer the prospect of, someday, being able to manipulate stress-hormone levels to improve patients' recovery from surgery or wounds or their responses to vaccines.

You've heard it a thousand times: Stress is bad for you. And it's certainly true that chronic stress, lasting weeks and months, has deleterious effects including, notably, suppression of the immune response. But short-term stress — the fight-or-flight response, a mobilization of bodily resources lasting minutes or hours in response to immediate threats — stimulates immune activity, said lead author Firdaus Dhabhar, PhD, an associate professor of psychiatry and behavioral sciences and member of the Stanford Institute for Immunity, Transplantation, and Infection.

And that's a good thing. The immune system is crucial for wound healing and preventing or fighting infection, and both wounds and infections are common risks during chases, escapes and combat.

Working with colleagues at Stanford and two other universities in a study to be published online June 22 in the Journal of Psychoneuroendocrinology, Dhabhar showed that subjecting laboratory rats to mild stress caused a massive mobilization of several key types of immune cells into the bloodstream and then onto destinations including the skin and other tissues. This large-scale migration of immune cells, which took place over a time course of two hours, was comparable to the mustering of troops in a crisis, Dhabhar said. He and colleagues had previously shown that a similar immune-cell redistribution in patients experiencing the short-term stress of surgery predicts enhanced postoperative recovery.

In the new study, the investigators were able to show that the massive redistribution of immune cells throughout the body was orchestrated by three hormones released by the adrenal glands, in different amounts and at different times, in response to the stress-inducing event. These hormones are the brain's call-to-arms to the rest of the body, Dhabhar said.

"Mother Nature gave us the fight-or-flight stress response to help us, not to kill us," said Dhabhar, who has been conducting experiments for well over a decade on the effects of the major stress hormones on the immune system. Last summer, Dhabhar received the International Society for Psychoneuroendocrinology's Curt. P. Richter Award for his work in this area, culminating in the new study.

The findings paint a clearer picture of exactly how the mind influences immune activity. "An impala's immune system has no way of knowing that a lion is lurking in the grass and is about to pounce, but its brain does," Dhabhar said. In such situations, it benefits lion and impala alike when pathogen-fighting immune cells are in positions of readiness in such places as the skin and mucous membranes, which are at high risk for damage and consequent infection.

So it makes perfect evolutionary sense that predator/prey activity and other situations in nature, such as dominance challenges and sexual approaches, trigger stress hormones. "You don't want to keep your immune system on high alert at all times," Dhabhar said. "So nature uses the brain, the organ most capable of detecting an approaching challenge, to signal that detection to the rest of the body by directing the release of stress hormones. Without them, a lion couldn't kill, and an impala couldn't escape." The stress hormones not only energize the animals' bodies — they can run faster, jump higher, bite harder — but, it turns out, also mobilize the immune troops to prepare for looming trouble.

The response occurs across the animal kingdom, he added. You see pretty much the same pattern of hormone release in a fish that has been picked up out of the water.

The experiments in this study were performed on rats, which Dhabhar subjected to mild stress by confining them (gently, and with full ventilation) in transparent Plexiglas enclosures to induce stress. He drew blood several times over a two-hour period and, for each time point, measured levels of three major hormones — norepinephrine, epinephrine and corticosterone (the rat analog of cortisol in humans) — as well as of several distinct immune-cell types in the blood.

What he saw was a pattern of carefully choreographed changes in blood levels of the three hormones along with the movement of many different subsets of immune cells from reservoirs such as the spleen and bone marrow into the blood and, finally, to various "front line" organs.

To show that specific hormones were responsible for movements of specific cell types, Dhabhar administered the three hormones, separately or in various combinations, to rats whose adrenal glands had been removed so they couldn't generate their own stress hormones. When the researchers mimicked the pattern of stress-hormone release previously

observed in the confined rats, the same immune-cell migration patterns emerged in the rats without adrenal glands. Placebo treatment produced no such effect.

The general pattern, Dhabhar said, was that norepinephrine is released early and is primarily involved in mobilizing all major immune-cell types — monocytes, neutrophils and lymphocytes — into the blood. Epinephrine, also released early, mobilized monocytes and neutrophils into the blood, while nudging lymphocytes out into "battlefield" destinations such as skin. And corticosterone, released somewhat later, caused virtually all immune cell types to head out of circulation to the "battlefields."

The overall effect of these movements is to bolster immune readiness. A study published by Dhabhar and his colleagues in 2009 in the Journal of Bone and Joint Surgery assessed patients' recovery from surgery as a function of their immune-cell redistribution patterns during the stress of the operation. Those patients in whom the stress of surgery mobilized immune-cell redistributions similar to those seen in the confined rats in the new study did significantly better afterward than patients whose stress hormones less adequately guided immune cells to appropriate destinations.

The mechanisms Dhabhar has delineated could lead to medical applications, such as administering low doses of stress hormones or drugs that mimic or antagonize them in order to optimize patients' immune readiness for procedures such as surgery or vaccination. "More studies will be required including in human subjects, which we hope to conduct, before these applications can be attempted," Dhabhar said. Closer at hand is the monitoring of patients' stress-hormone levels and immune-cell distribution patterns during surgery to assess their surgical prognosis, or during immunization to predict vaccine effectiveness.

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