

Bone, not adrenaline, drives fight or flight response

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When faced with a predator or sudden danger, the heart rate goes up, breathing becomes more rapid, and fuel in the form of glucose is pumped throughout the body to prepare an animal to fight or flee.

These physiological changes, which constitute the "fight or flight" response, are thought to be triggered in part by the hormone adrenaline.

But a new study from Columbia researchers suggests that bony vertebrates can't muster this response to danger without the [skeleton](#). The researchers found in mice and humans that almost immediately after the brain recognizes danger, it instructs the skeleton to flood the bloodstream with the bone-derived hormone osteocalcin, which is needed to turn on the fight or flight response.

"In bony vertebrates, the acute [stress](#) response is not possible without osteocalcin," says the study's senior investigator Gérard Karsenty, MD, Ph.D., chair of the Department of Genetics and Development at Columbia University Vagelos College of Physicians and Surgeons.

"It completely changes how we think about how acute stress responses occur."

Why Bone?

"The view of bones as merely an assembly of calcified tubes is deeply entrenched in our biomedical culture," Karsenty says. But about a decade ago, his lab hypothesized and demonstrated that the skeleton has hidden influences on other organs.

The research revealed that the skeleton releases osteocalcin, which travels through the bloodstream to affect the functions of the biology of the pancreas, the brain, muscles, and other organs.

A series of studies since then have shown that osteocalcin helps regulate metabolism by increasing the ability of cells to take in glucose, improves memory, and helps animals run faster with greater endurance.

Why does bone have all these seemingly unrelated effects on other organs?

"If you think of bone as something that evolved to protect the organism from danger—the skull protects the brain from trauma, the skeleton allows vertebrates to escape predators, and even the bones in the ear alert us to approaching danger—the hormonal functions of osteocalcin begin to make sense," Karsenty says. If bone evolved as a means to escape danger, Karsenty hypothesized that the skeleton should also be involved in the acute stress response, which is activated in the presence of danger.

Osteocalcin Necessary to React to Danger

If osteocalcin helps bring about the acute stress response, it must work fast, in the first few minutes after danger is detected.

In the new study, the researchers presented mice with predator urine and other stressors and looked for changes in the bloodstream. Within 2 to 3 minutes, they saw osteocalcin levels spike.

Similarly in people, the researchers found that osteocalcin also surges in people when they are subjected to the stress of public speaking or cross-examination.

When osteocalcin levels increased, [heart rate](#), body temperature, and blood glucose levels in the mice also rose as the fight or flight response kicked in.

In contrast, mice that had been genetically engineered so that they were unable to make osteocalcin or its receptor were totally indifferent to the stressor. "Without osteocalcin, they didn't react strongly to the perceived danger," Karsenty says. "In the wild, they'd have a short day."

As a final test, the researchers were able to bring on an acute stress response in unstressed mice simply by injecting large amounts of osteocalcin.

Adrenaline Not Necessary for Fight or Flight

The findings may also explain why animals without [adrenal glands](#) and adrenal-insufficient patients—with no means of producing adrenaline or other adrenal hormones—can develop an acute stress response.

Among mice, this capability disappeared when the mice were unable to produce large amounts of osteocalcin.

"This shows us that circulating levels of osteocalcin are enough to drive the acute stress response," says Karsenty.

Physiology the New Frontier of Biology

Physiology may sound like old-fashioned biology, but new genetic techniques developed in the last 15 years have established it as a new frontier in science.

The ability to inactivate single genes in specific cells inside an animal, and at specific times, has led to the identification of many new inter-organ relationships. The skeleton is just one example; the heart and muscles are also exerting influence over other organs.

"I have no doubt that there are many more new inter-organ signals to be discovered," Karsenty says, "and these interactions may be as important as the ones discovered in the early part of the 20th century."

The study, "Mediation of the acute stress response by the skeleton," was

published Sept. 12 in *Cell Metabolism*.

More information: "Mediation of the acute stress response by the skeleton," *Cell Metabolism* (2019). DOI: [10.1016/j.cmet.2019.08.012](https://doi.org/10.1016/j.cmet.2019.08.012) , [https://www.cell.com/cell-metabolism/fulltext/S1550-4131\(19\)30441-3](https://www.cell.com/cell-metabolism/fulltext/S1550-4131(19)30441-3)

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