Study shows benefits of hormone found in fat tissue

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It's called the obesity paradox. Although obese people are more apt to suffer from inflammatory diseases, such as diabetes, heart disease, and stroke, they are also more likely to survive a major attack caused by one of those conditions.

University of Illinois scientists Gregory Freund and Christina Sherry shed light on the reasons for this phenomenon in a study in this month's issue of *Endocrinology*.

"Fat is a very complex and active tissue—it has important functions beyond providing energy and insulating us from the cold," said Freund, a professor in the U of I College of Medicine's Department of Pathology and a faculty member in the U of I Division of Nutritional Sciences.

"We now know that leptin, a hormone secreted by fat tissue, plays a key role in regulating the immune system. When we exposed mice to hypoxia (simulating an event, such as a heart attack, in which a part of the body is deprived of oxygen), leptin triggered the immune system to increase production of an anti-inflammatory molecule, interleukin-1 receptor antagonist (IL-1RA)," he said.

"And, when we gave non-obese mice leptin injections, they recovered three times faster. Leptin did not hasten recovery though in IL-1RA knockout mice," Sherry said. That earlier work was published in a recent issue of *Brain, Behavior, and Immunity*.

In the *Endocrinology* study, one group of mice was fed a high-fat diet for 12 weeks (Sherry described this group as being in a mildly obese, pre-diabetic state), while another group was fed a normal diet. The obese mice recovered from acute hypoxia five times faster than the mice fed normal diets.

In a second experiment, Freund and Sherry examined macrophages (or immune cells) that were resident in peritoneal fat tissue from both groups of mice. In mice fed the high-fat diet, there was a very significant increase in IL-1RA as compared to mice fed the normal diet (330 pg vs.15 pg).

"Our hypothesis is that the macrophages from animals fed the high-fat diet are making more IL-1RA because they're 'living' in an environment of significantly increased leptin. Obesity can be considered a state of hyperleptinemia," said Sherry.

The scientists then isolated the stromal vascular fraction of the fat tissue—which contains the macrophages—from three obese mice and injected it into the peritoneal cavity of a normal mouse. "Within 3 hours we saw an 836 percent increase in the IL-1RA serum level of the normal mouse and an accelerated recovery from hypoxia," Sherry said.

To confirm that IL-1RA was implicated in this accelerated recovery, normal mice were given injections of IL-1RA, and their recovery matched that of mice fed the high-fat diet.

Finally, Freund and Sherry injected IL-1RA antiserum into the obese animals an hour before exposing them to hypoxia.

"We expected the antibodies to bind all the IL-1RA so it couldn't affect recovery," she said. "And, sure enough, these animals didn't recover until 6 hours after the hypoxic event, basically the same pattern we saw with

non-obese animals."

"So we were able to prove through several different mechanisms that in cases of obesity, there's a significant increase in the anti-inflammatory molecule IL-1RA, which helps animals recover from a traumatic loss of oxygen. The obese mice recovered faster because of the leptin-induced increase in IL-1RA," said Sherry.

Sherry repeated that obesity is a predisposing factor in many inflammatory conditions and encouraged people who are at a healthy weight to maintain that weight.

"However, obese persons do have about six times more circulating IL-1RA, which again is the anti-inflammatory molecule that aids recovery in oxygen-starved parts of the body," she noted.

"Once a health problem is established, there are certain conditions—congestive heart failure, rheumatoid arthritis, and other diseases that involve the utilization of oxygen—in which obese persons have been shown to have a better prognosis. And there is a legitimate discussion among physicians about how such patients should deal with their excess weight," said Freund.

More information: Stephanie Kim of the U of I College of Medicine's Department of Pathology co-authored the Endocrinology study. Jason M. Kramer, also of the U of I College of Medicine's Department of Pathology, and Jason M. York of the U of I Department of Animal Sciences, are co-authors of the Brain, Behavior, and Immunity paper.

Source: University of Illinois at Urbana-Champaign