Loss of weight associated with chronic illness may soon have first treatment

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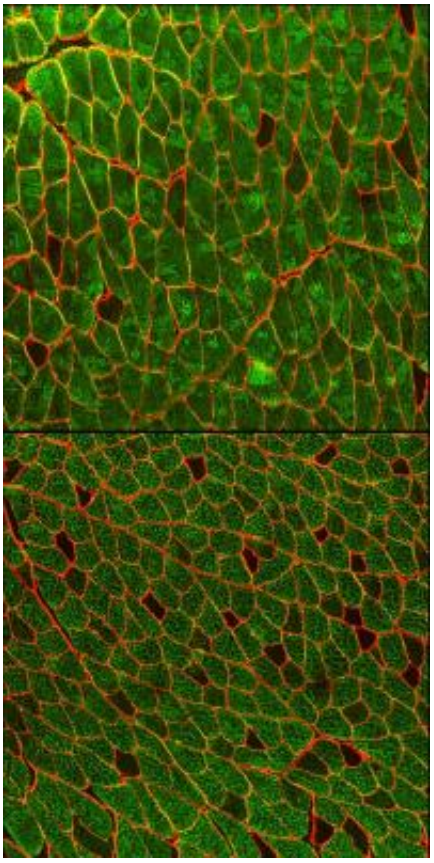

Scientists at OHSU Doernbecher found the muscle of rodents with isolated inflammation in the brain undergoes rapid atrophy. This process, they discovered, leads to the rapid release of cortisol into the blood, which acts on muscle to elicit wasting (top photo: normal muscle fibers; bottom photo: atrophied muscle fibers as a result of brain inflammation, release of cortisol). Credit: Oregon Health & Science University Doernbecher Children's Hospital

Patients with cancer, heart disease and other chronic illness struggle not only with complications inherent to their disease, they also experience an involuntary loss of weight and muscle mass triggered by the body's natural response to infection and inflammation. Increasing nutrition intake does not mitigate the process and there is no treatment.

Today scientists at Oregon Health & Science University Doernbecher Children's Hospital report they have discovered a definitive role for the brain in regulating loss of muscle mass that previously has not been described. The process is driven by a signaling system in the brain that controls stress responses and the release of the stress hormone cortisol. This finding is of particular significance because many drugs that regulate the release of cortisol are now in development for the treatment of other conditions.

"The wasting associated with chronic illness has been recognized since the time of the ancient Greeks. Despite this long history, no effective treatments currently are available that can reverse muscle wasting," said Daniel L. Marks, M.D., Ph.D., principal investigator and associate professor of pediatrics in the Papé Family Pediatric Research Institute at OHSU Doernbecher Children's Hospital.

"Not only does wasting negatively affect quality of life, but it also significantly impacts mortality in patients with chronic illness. Our lab has found that the system by which our brains mediate the response to stressful stimuli is critical in regulating the loss of muscle mass that accompanies disease," Marks said.

In response to infection, the body mobilizes protein stored in the muscle to fuel the immune system. This process is critical in the response to acute infection, but when it occurs excessively, as in the case of chronic disease, profound loss of muscle mass and weakness result.

Theodore Braun, a Ph.D. candidate in the Marks lab, and colleagues found that the muscle of rodents with isolated inflammation in the brain undergoes rapid atrophy. This process, they discovered, leads to the rapid release of cortisol into the blood, which acts on muscle to elicit wasting. When this system is blocked, the muscle mass loss in response to inflammation is prevented. Furthermore, when cortisol was infused at a level mimicking the production that occurs in many chronic diseases, dramatic muscle wasting results.

Because the prevention of muscle mass loss in response to cancer growth recently has been shown to improve survival in mice, the researchers suggest that targeting this system could improve quality of life and reduce mortality associated with chronic disease.

The study, "Central nervous system inflammation induces muscle atrophy via activation of the hypothalamic-pituitary-adrenal axis," was funded by the Canadian Institutes of Health Research and the National Institutes of Health and is published in today's The *Journal of Experimental Medicine*.

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