MedicalXpress

Gatekeeper of brain steroid signals boosts emotional resilience to stress

April 23 2012

A cellular protein called HDAC6, newly characterized as a gatekeeper of steroid biology in the brain, may provide a novel target for treating and preventing stress-linked disorders, such as depression and post-traumatic stress disorder (PTSD), according to research from the Perelman School of Medicine at the University of Pennsylvania.

Glucocorticoids are natural steroids secreted by the body during stress. A small amount of these hormones helps with normal brain function, but their excess is a precipitating factor for stress-related disorders.

Glucocorticoids exert their effects on mood by acting on receptors in the nucleus of emotion–regulating neurons, such as those producing the neurotransmitter serotonin. For years, researchers have searched for ways to prevent deleterious effects of stress by blocking glucocorticoids in neurons. However, this has proved difficult to do without simultaneously interfering with other functions of these hormones, such as the regulation of immune function and energy metabolism.

In a recent *Journal of Neuroscience* paper, the lab of Olivier Berton, PhD, assistant professor of Psychiatry, shows how a regulator of glucocorticoid receptors may provide a path towards resilience to stress by modulating glucocorticoid signaling in the brain. The protein HDAC6, which is particularly enriched in serotonin pathways, as well as in other mood-regulatory regions in both mice and humans, is ideally distributed in the brain to mediate the effect of glucocorticoids on mood and emotions. HDAC6 likely does this by controlling the interactions

between glucocorticoid receptors and hormones in these serotonin circuits.

Experiments that first alerted Berton and colleagues to a peculiar role of HDAC6 in stress adaptation came from an approach that reproduces certain clinical features of traumatic stress and depression in mice. The animals are exposed to brief bouts of aggression from trained "bully" mice. In most aggression-exposed mice this experience leads to the development of a lasting form of social aversion that can be treated by chronic administration of antidepressants.

In contrast, a portion of mice exposed to chronic aggression consistently express spontaneous resilience to the stress and do not develop any symptoms. By comparing gene expression in the brains of spontaneously resilient and vulnerable mice, Berton and colleagues discovered that reducing HDAC6 expression is a hallmark of naturally resilient animals. While aggression also caused severe changes in the shape of serotonin neurons and their capacity to transmit electrical signals in vulnerable mice, stress-resilient mice, in contrast, escaped most of these neurobiological changes.

To better understand the link between HDAC6 and the development of stress resilience, Berton and colleagues devised a genetic approach to directly manipulate HDAC6 levels in neurons: Deletion of HDAC6 in serotonin neurons -- the densest HDAC6-expressing cell group in the mouse brain -- dramatically reduced social and anxiety symptoms in mice exposed to bullies and also fully prevented neurobiological changes due to stress, fully mimicking a resilient phenotype.

Using biochemical assays, Berton's team showed it is by promoting reversible chemical changes onto a heat shock chaperone protein, Hsp90, that HDAC6 deletion is able to literally switch off the effects of glucocorticoid hormones on social and anxiety behaviors.

Chaperones are proteins that help with the folding or unfolding and the assembly or disassembly of protein complexes. The way in which glucocorticoid receptor chaperoning and stress are linked is not well understood. Yet, genetic variations in certain components of the glucocorticoid receptor chaperone complex have been associated with the development of stress-related disorders and individual variability in therapeutic responses to antidepressants.

"We provide pharmacological and genetic evidence indicating that HDAC6 controls certain aspects of Hsp90 structure and function in the brain, and thereby modulates protein interactions, as well as hormone- and stress-induced glucocorticoid receptor signaling and behavior," explains Berton.

Together, these results identify HDAC6 as a possible stress vulnerability biomarker and point to pharmacological inhibition of HDAC6 as a potential new strategy for antidepressant interventions through regulation of Hsp90 in glucocorticoid signaling in serotonin neurons.

Provided by University of Pennsylvania School of Medicine

Citation: Gatekeeper of brain steroid signals boosts emotional resilience to stress (2012, April 23) retrieved 25 April 2024 from https://medicalxpress.com/news/2012-04-gatekeeper-brain-steroid-boosts-emotional.html