Researchers identify potential treatment for cognitive effects of stress-related disorders

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Columbia University Medical Center (CUMC) researchers have identified a potential medical treatment for the cognitive effects of stress-related disorders, including post-traumatic stress disorder (PTSD). The study, conducted in a PTSD mouse model, shows that an experimental drug called S107, one of a new class of small-molecule compounds called Rycals, prevented learning and memory deficits associated with stress-related disorders. The findings were published today in the online edition of *Cell*.

"With the dramatic rise in cases of PTSD among our combat veterans, and following common afflictions such as heart attacks, there is a pressing need for new and better therapies for this debilitating disorder," said study leader Andrew R. Marks, MD, chair and professor of physiology and cellular biophysics, the Clyde and Helen Wu Professor of Medicine, and director of the Wu Center for Molecular Cardiology at CUMC. "Our study provides new insight regarding the mechanism of stress-related cognitive disorders, as well as a potential treatment based on the understanding of this mechanism."

PTSD is a disabling anxiety disorder triggered by a traumatic experience, ranging from a one-time event such as physical assault to chronic stresses such as those experienced during warfare. Patients are commonly treated with supportive therapies, including antipsychotics, antidepressants, anti-anxiety medications, and psychotherapy. However, there is currently no specific treatment for PTSD and related disorders.

Several studies have shown that chronic stress could affect the structure and function of neurons in the brain. Researchers have proposed that these effects could contribute to neuropsychiatric disorders, including PTSD, which involves symptoms of cognitive dysfunction. However, exactly how the cognitive dysfunction arises (which manifests as impaired learning and memory) has not been clear.

Based on his earlier work in heart and muscle disorders, Dr. Marks reasoned that chronic stress could lead to PTSD by destabilizing type 2 ryanodine receptors (RyR2) in the hippocampus, the brain region that plays a central role in learning and memory. RyR2 are channels that regulate the level of calcium in neurons, which is vital to cell survival and function.

In earlier mouse studies, Dr. Marks and his team showed that stress can cause RyR2 channels in heart muscle to leak calcium resulting in heart failure and arrhythmias. Subsequent studies in mouse models conducted by Dr. Marks' lab showed that leaky RyR1 channels (a closely related calcium channel) in skeletal muscle can contribute to Duchenne muscular dystrophy, limb-girdle muscular dystrophy and age-related muscle weakness.

To ascertain whether leaky RyR2 channels are a factor in stress-related cognitive disorders, the researchers used a classic model for PTSD that involves subjecting mice to stressful conditions for three weeks. This raises their corticosteroid levels (a classic marker of stress) and activates genes known to be expressed in response to stress.

"When we examined the hippocampal neurons of the stressed mice, we found that their RyR2 channels had become destabilized and leaky compared with channels from normal non-stressed mice which were not leaky. There was a remodeling of the channels that we had previously seen in heart and skeletal muscles from animal models of chronic

diseases including heart failure and muscular dystrophy. We found these same leaky channels in samples from patients with these disorders but not in those from healthy humans," said Dr. Marks.

"The next question was: Do the leaky channels affect memory and learning, two functions that are impaired in individuals with PTSD?" said Dr. Marks. "Using classic behavioral and cognitive function tests, including a water-maze and object-recognition tests, we found that the stressed mice developed profound cognitive abnormalities affecting both learning and memory."

The researchers confirmed that hippocampal RyR2 channels were involved in the cognitive decline of the mice in two ways. First, when the mice were given Rycal S107, a novel drug designed in Dr. Marks' lab that prevents the calcium leak by stabilizing RyR2 channels, cognitive function was not affected by exposure to chronic stress. Second, the researchers created a strain of mice in which stress signals cannot destabilize hippocampal RyR2 channels. When these mice were subjected to chronic stress, they showed no signs of cognitive impairment.

Dr. Marks expects that clinical trials with S107, or a similar Rycal, for the treatment of PTSD could begin within several years. Another Rycal is currently being tested in patients with heart failure and arrhythmias.

The researchers are also examining the role of these RyR2 channels in neurodegenerative diseases, including Alzheimer's.

More information: Dr. Marks' paper is titled, "Role of Leaky Neuronal Ryanodine Receptors in Stress-Induced Cognitive Dysfunction."