Neuron-based gene expression study reveals insights on fear and its regulation

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Researcher led by a team at McLean has found a potential new target for diagnosing, treating, and preventing fear-related psychiatric illnesses Credit: McLean Hospital

Fear and fear extinction learning (the gradual reduction of fear by repeated exposure to the feared object) are adaptive processes caused by molecular changes in specific brain circuits, and they're perturbed in conditions such as anxiety and post-traumatic stress disorder. A new

study by investigators at McLean Hospital and Massachusetts General Hospital reveals that the expression of a particular gene may function as a switch to regulate feelings of fear and its extinction. The findings point to a potential new target for diagnosing, treating, and preventing fear-related psychiatric illnesses.

The research, which is published in *Nature Communications*, focuses on neurons in the central amygdala that produce a corticotropin-releasing hormone (Crh) and are involved in the brain's response to threats. The scientists examined how different gene pathways are activated within Crh neurons after the expression or extinction of fear.

"This precise analysis utilized a new cell-type-specific technology called translating ribosome affinity purification, or TRAP, to identify gene expression only within the Crh amygdala cells," said co-senior author Nikolaos P. Daskalakis, MD, Ph.D., who is the director of the Neurogenomics and Translational Bioinformatics Laboratory at McLean Hospital. "The results showed that diverse gene networks are activated or inhibited by fear versus extinction learning."

Additional analyses demonstrated that fear extinction learning requires that Crh neurons reduce their expression of a regulatory gene named CREB, which codes for a protein called cAMP response-element binding protein. Indeed, overexpression of CREB in Crh neurons in mice increased their fear response.

"CREB is well known to be involved in learning and memory, and these data suggest that it may act as a molecular switch that regulates expression of fear and its extinction," said co-senior author Kerry J. Ressler, MD, Ph.D., McLean's chief scientific officer, McLean's chief of the Center of Excellence in Depression and Anxiety Disorders, and co-director of the Silvio O. Conte Center for Stress Peptide Advanced Research, Education & Dissemination (SPARED) at McLean Hospital.

Targeting CREB expression in Crh neurons in the brain's amygdala may provide a better understanding of the mechanisms behind fear-based psychiatric illnesses and represent a promising treatment strategy.

"Fear is one of the most basic emotions we all experience in response to trauma—and also one of the most complex to study," says Magali Haas, MD, Ph.D., CEO and president of Cohen Veterans Bioscience, the nonprofit biotech research organization fast-tracking diagnostics and therapeutics for trauma-related and other brain disorders. "We are proud to support this latest research into how animal models' brains process fear, which could provide important parallels in humans and lead to new ways to diagnose or treat disorders such as PTSD."

More information: Kenneth M. McCullough et al, Genome-wide translational profiling of amygdala Crh-expressing neurons reveals role for CREB in fear extinction learning, *Nature Communications* (2020). DOI: 10.1038/s41467-020-18985-6

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