Mechanism sheds light on how the brain adapts to stress

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Scientists now have a better understanding of the way that stress impacts the brain. New research, published by Cell Press in the January 26 issue of the journal *Neuron*, reveals pioneering evidence for a new mechanism of stress adaptation and may eventually lead to a better understanding of why prolonged and repeated exposure to stress can lead to anxiety disorders and depression.

Most stressful stimuli cause the release of corticotropin-releasing hormone (CRH) from neurons in the brain. This is typically followed by rapid changes in CRH gene expression. In more practical terms, as soon as the CRH-containing neurons run out of CRH, they are already receiving directions to make more. CRH controls various reactions to stress, including immediate "fight-or-flight" responses as well as more delayed adaptive responses in the brain. Regulation of CRH activity is critical for adaptation to stress, and abnormal regulation of CRH is linked with multiple human psychiatric disorders.

"Despite the wealth of information regarding the physiological role of CRH in mediating the response to stress, the molecular mechanisms that regulate expression of the CRH gene, and thereby CRH synthesis, have remained largely elusive," explains senior study author, Dr. Gil Levkowitz, from the Weizmann Institute of Science in Israel. "In our study, we used mouse and zebrafish model systems to identify a novel intracellular signaling pathway that controls stress-induced CRH gene expression."

Dr. Levkowitz and colleagues discovered that the protein Orthopedia (Otp), which is expressed in parts of the brain associated with stress adaptation, modulated CRH gene expression and was required for stress adaptation. The researchers went on to show that Otp regulates production of two different receptors on the neurons' surface. The receptors, which receive and relay CRH production instructions, essentially function as "ON" and "OFF" switches.

"This regulation of the CRH gene is critical for neuronal adaptation to stress. Failure to activate or terminate the CRH response can lead to chronic over- or under-activation of stress-related brain circuits, leading to pathological conditions," concludes Dr. Levkowitz. "Taken together, our findings identify an evolutionarily conserved biochemical pathway that modulates adaptation to stress."

More information: Amir-Zilberstein et al.: “Homeodomain protein Otp and activity-dependent splicing modulate neuronal adaptation to stress.” *Neuron*, January 26, 2012.

Abstract

Regulation of corticotropin-releasing hormone (CRH) activity is critical for the animal’s adaptation to stressful challenges, and its dysregulation is associated with psychiatric disorders in humans. However, the molecular mechanism underlying this transcriptional response to stress is not well understood. Using various stress paradigms in mouse and zebrafish, we show that the hypothalamic transcription factor Orthopedia modulates the expression of CRH as well as the splicing factor Ataxin 2-Binding Protein-1 (A2BP1/Rbfox-1). We further show that the G protein coupled receptor PAC1, which is a known A2BP1/Rbfox-1 splicing target and an important mediator of CRH activity, is alternatively spliced in response to a stressful challenge. The generation of PAC1-hop messenger RNA isoform by alternative splicing is required for termination of CRH transcription, normal activation of the

hypothalamic-pituitary-adrenal axis and adaptive anxiety-like behavior. Our study identifies an evolutionarily conserved biochemical pathway that modulates the neuronal adaptation to stress through transcriptional activation and alternative splicing.

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