Epigenetics contribute to male and female differences in fear memory

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In a mouse model of traumatic memory, male mice recall fear-related memories better than female mice, according to a study in *Biological Psychiatry*. The difference between sexes was attributed to a gene important for creating fear memories and stress behavior, called cyclin dependent kinase 5 (*Cdk5*), which was naturally activated in male but not in female mice. The findings could help explain why fear and stress-related disorders affect men and women differently.

Fear and memory produce changes to genes that modulate gene expression, called epigenetic modifications. Epigenetic activation of *Cdk5* increased naturally in males, but not in females, after the mice recalled a fear-related memory. Artificial activation of *Cdk5* had no effect in male mice, in which *Cdk5* was already naturally increased, but reduced the strength of fear memories in female mice, indicating sex differences in how fear is remembered.

"There is growing evidence for sex differences in the neurobiology of fear. These differences may provide important new insights into novel sex-specific treatments for anxiety disorders," said John Krystal, MD, Editor of *Biological Psychiatry*.

Although previous research had already shown that *Cdk5* is activated by stress and regulates the strength of fear-related memories, it had only been studied in male mice. "We examined both sexes, and found male-specific epigenetic activation of *Cdk5* expression after fear conditioning, a model of traumatic memory," said senior author Elizabeth A. Heller, Ph.D., University of Pennsylvania.

Dr. Heller and colleagues then used epigenetic editing to artificially increase *Cdk5* activation in the hippocampus, the brain's memory hub. "Remarkably, this manipulation reduced fear memory retrieval and increased Tau phosphorylation in female, but not male mice," said Dr. Heller. Phosphorylation of the protein tau by *Cdk5* regulates learning and memory.

"Taken together, epigenetic editing uncovered a female-specific role of *Cdk5* activation in repressing fear-induced memory," said Dr. Heller. *Cdk5* activation and tau phosphorylation have been shown to cause negative effects on learning and memory in female mice, but not male mice. The authors suggest that *Cdk5* expression is naturally blocked in females to protect them from these negative effects.

The epigenetic differences in male and female mice indicate sex differences in the biology of how fearful events are remembered, which highlights that sex should be an important consideration in the research and treatment of neuropsychiatric diseases that involve fear and stress, such as posttraumatic stress disorder, depression, and anxiety.

More information: Ajinkya S. Sase et al. Sex-Specific Regulation of Fear Memory by Targeted Epigenetic Editing of Cdk5, *Biological Psychiatry* (2018). DOI: 10.1016/j.biopsych.2018.11.022

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