Getting on 'the GABA receptor shuttle' to treat anxiety disorders

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There are increasingly precise molecular insights into ways that stress exposure leads to fear and through which fear extinction resolves these fear states. Extinction is generally regarded as new inhibitory learning, but where the inhibition originates from remains to be determined. Gamma-aminobutyric acid (GABA), the primary inhibitory chemical messenger in the brain, seems to be very important to these processes.

A new article in Biological Psychiatry examined whether during the extinction of fear learning, GABA receptors may be inserted into the cell surface to reduce the excitability of the amygdala. Researchers inactivated a protein that links GABAA receptors to the cell surface. They found that this protein prevented fear extinction training and the local application of NMDA from increasing the number of GABAA receptors on the cell surface and enhancing the inhibition of amygdala nerve cells.

Lin and colleagues show that during fear conditioning, the number of GABAA receptors on the surface of neurons in the amygdala decreases, reducing the extent of inhibition of the neurons in this brain "fear center." When fear is extinguished by dissociating fear cues from unpleasant stimuli, the number of GABAA receptors on the cell surface of the amygdala neurons increases.

How does this happen? The study provides evidence of molecular mechanisms that shuttle GABAA receptors to the cell surface during extinction. The researchers showed that by inactivating a protein

involved in the localization of GABAA receptors in the amygdala, they prevented the recruitment of GABA-mediated inhibition and extinction of fear. Dr. John Krystal, Editor of *Biological Psychiatry* comments: "This research provides evidence that we are starting to untangle the molecular mechanisms through which our cognitive and behavioral therapies might alter brain function."

More information: The article is "Block of γ-Aminobutyric Acid-A Receptor Insertion in the Amygdala Impairs Extinction of Conditioned Fear" by Hui-Ching Lin, Sheng-Chun Mao, and Po-Wu Gean. The authors are affiliated with the Institute of Basic Medical Sciences and Department of Pharmacology, Center for Gene Regulation and Signal Transduction Research, National Cheng Kung University, Tainan, Taiwan. The article appears in *Biological Psychiatry*, Volume 66, Issue 7 (October 1, 2009), published by Elsevier.

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