Reversal of Pain and Affective Comorbidities by Rebalancing Mutual Inhibitory Amygdala Circuits

Yu-Ling Lin,[1] Wai-Yi Wong,[1] Shuu-Jiun Wang,[1,2,4,6] Shih-Pin Chen,[1,2,3,4,5,6] Jen-Kun Cheng,[7,8] Hui Lu,[9] and Cheng-Chang Lien[1,2*]

[1]Institute of Neuroscience, National Yang-Ming University, Taipei 112, Taiwan

[2]Brain Research Center, National Yang-Ming University, Taipei 112, Taiwan

[3]Institute of Clinical Medicine, National Yang-Ming University, Taipei 112, Taiwan

[4]Department of Neurology, Neurological Institute, Taipei Veterans General Hospital, Taipei 112, Taiwan

[5]Division of Translational Research, Department of Medical Research, Taipei Veterans General Hospital, Taipei 112, Taiwan

[6]Faculty of Medicine, National Yang-Ming University, Taipei 112, Taiwan

[7]Department of Medicine, Mackay Medical College, New Taipei 252, Taiwan

[8]Department of Anesthesiology, Mackay Memorial Hospital, Taipei 104, Taiwan

[9]Department of Pharmacology and Physiology, George Washington University, Washington, DC 20037, USA

Chronic pain is associated with neuropsychiatric comorbidities. Although the amygdala emerges as a site for linking affect and nociception, the mechanisms by which the two dimensions are regulated at the circuit level remain unestablished. Using a mouse model of chronic muscle pain, we show that opposing pain-related neuroplasticity occurs in genetically distinct central amygdala (CeA) neurons. In these mice, somatostatin (SST)-expressing neurons were hyperexcitable and received enhanced excitatory transmission, whereas PKCδ-expressing neurons were less excitable and received weakened excitatory transmission. Chemogenetic manipulations of these neurons revealed that the balance of activity between these two neurons determines pain-related behaviors. Accordingly, decreasing the activity ratio of CeA-SST to CeA-PKCδ neurons alleviated pain and affective comorbidities in mice with chronic pain. Conversely, increasing the activity ratio was sufficient to induce tactile hypersensitivity in healthy mice. Thus, reversing imbalanced CeA circuits may be a novel therapeutic strategy for chronic pain and its related affective disorders.