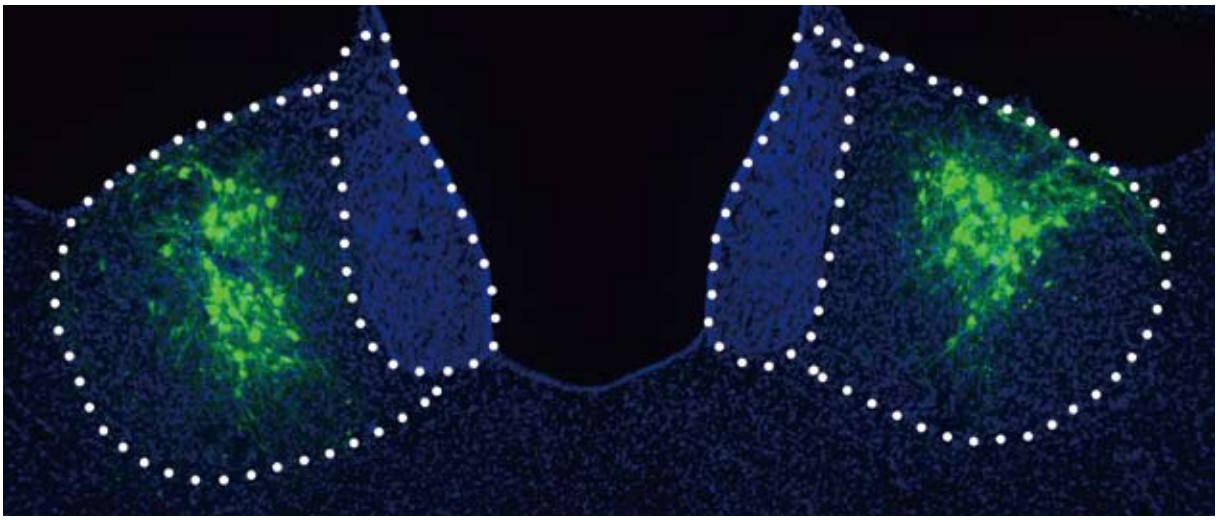
# New Molecular Mechanism of Depression Revealed

Major depressive disorder (MDD) is one of the most prevalent and disabling mental disorders, affecting more than 10% of populations worldwide. Modern views on the pathogenesis of MDD suggest that the neural activity of specific brain circuits are altered in response to external stimuli, such as stress, as a result of maladaptive molecular and cellular changes.

Recently, the lateral habenula (LHb) has emerged as a key brain region in aversive behaviors and the pathophysiology of depression. Neuroimaging studies have identified heightened habenula activity in the depressed state. However, what molecular mechanisms underlie these aberrant cellular processes in LHb and how depression-inducing stimuli lead to these changes were largely unknown.

To address this problem, LI Kun and ZHOU Tao from HU Hailan's lab at the Institute of Neuroscience (ION), Shanghai Institutes for Biological Sciences, CAS took an unbiased, mass spectrometry-based, quantitative proteomic screening, to compare the protein content of LHb in the

A latest study from HU Hailan's research group found that βCaMKII expression in lateral habenula plays a critical role in depression. Lateral habenula (in green) and mice under two emotional states are depicted in the figure.



Using viral vector-based RNAi silencing to reduce βCaMKII expression in lateral habenula reversed depressive-like behaviors in congenital depressed rats. (Images by Dr. HU Hailan)

normal and congenital depressed rats. They discovered that a member of the calcium/calmodulin-dependent protein kinase type II family, βCaMKII, was significantly up-regulated in the habenula of different animal models of depression, whereas antidepressant treatment caused significant downregulation of βCaMKII protein in the habenula of rats with depression-like phenotypes.

Using viral vector-based and brain-region-specific gene manipulations, they found that overexpression of βCaMKII in the LHb of unstressed animals caused core symptoms of depression, including anhedonia (inability to feel pleasure) and behavioral despair. In contrast, downregulation of βCaMKII using RNAi in LHb reversed depression-like symptoms. Electrophysiological recordings revealed that LHb neurons overexpressing βCaMKII had enhanced synaptic efficacy and increased neuronal firing. Blockade of the function of GulR1, a molecule downstream of βCaMKII, prevented the depressive effects of βCaMKII overexpression. These findings uncovered new molecular mechanisms underlying the hyperactivity of habenula in depression and identified new molecular targets for gene therapy of depression.

This research entitled "βCaMKII in lateral habenula mediates core symptoms of depression" was published in *Science* on August 30, 2013. This work was mainly carried out by graduate students LI Kun and ZHOU Tao under the supervision of Dr. HU Hailan at ION. Dr. LIAO Lujian and Catherine Wong in John R. Yates' laboratory (Scripps Institute) performed the quantitative proteomic analysis. Dr. Fritz Henn (Cold Spring Harbor Laboratory) provided the congenitally depressed rats. Other collaborators include YANG Zhongfei (ION) and Roberto Malinow (UCSD).

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