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PSYCHIATRIC DISORDERS

Reining in the habenula?

The lateral habenula — a phylogenetically ancient brain structure — is hyperactive in individuals with depression and in animal models of this disorder. The causes of this hyperactivity and its relevance to the symptoms of depression have remained unclear, but Li *et al.* now provide evidence for a key role for β-calcium/calmodulin-dependent protein kinase type II (βCaMKII).

The authors first performed a proteome screen in habenulae from wild-type mice and congenitally learned helpless (cLH) mice — an established model of depression. This revealed that expression of βCaMKII was twice as high in the habenula of cLH mice. Similar increases in βCaMKII expression were found in two other mouse models of depression and, importantly, chronic treatment with the tricyclic antidepressant imipramine reduced βCaMKII levels in cLH mice.

Viral vector-mediated overexpression of βCaMKII in the lateral habenula resulted in depression-like behaviours, such as despair and anhedonia, in several tests in both mice and rats. Overexpression of a 'kinase-dead' version of βCaMKII in the lateral habenula did not induce depression-like behaviour, suggesting that its kinase function is involved in the induction of these behaviours. The authors next showed that reducing βCaMKII levels (through RNAi) or blocking the kinase function of βCaMKII (through viral expression of a dominant-negative, kinase-dead version of βCaMKII) in the lateral habenula of 'depressed' cLH rats reduced depression-like behaviour. Together, these findings in mice and rats indicate that increased βCaMKII expression — specifically, increased kinase function — in the lateral habenula is both sufficient and necessary for the expression of depression-like behaviour.

The authors performed electrophysiology experiments on lateral habenula slices from rats to investigate whether increased βCaMKII levels are associated with habenula hyperactivity like that found in depression. Neurons with virus-induced βCaMKII overexpression had a higher frequency and amplitude of miniature excitatory postsynaptic currents and a threefold higher spiking rate compared with that of non-infected neighbouring neurons. This indicates increased synaptic activity and increased output, respectively.

To identify the downstream targets of βCaMKII that may cause the hyperactivity of lateral habenula neurons, the authors measured the level of GluR1-type AMPA receptors (which is known to be upregulated by βCaMKII in hippocampal neurons). Western blot analysis showed that GluR1 levels were increased in the membrane fraction of the lateral habenula of cLH rats compared with those of control rats, and this effect was reduced after treatment with imipramine. Moreover, when the authors co-expressed βCaMKII and a dominant-negative form of GluR1 (which prevents synaptic insertion of GluR1) in the lateral habenula of mice, the mice did not show depression-like behaviour.

Together, these findings support a model in which upregulation of βCaMKII in the lateral habenula increases synaptic levels of GluR1, which causes hyperactivity of lateral habenula neurons. As the lateral habenula has several output regions, the resulting increased activity in these regions, including the ventral tegmental area, may underlie the different dimensions of depressive behaviour.

Leonie Welberg

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ORIGINAL RESEARCH PAPER Li, K. *et al.* βCaMKII in lateral habenula mediates core symptoms of depression. *Science* **341**, 1016–1020 (2013)
FURTHER READING Hikosaka, O. The habenula: from stress evasion to value-based decision-making. *Nature Rev. Neurosci.* **11**, 503–513 (2010)