Research Sheds Light on Cellular Basis of Depression

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Recent studies suggest that neurons in a particular area of the brain called the lateral habenula (LHb) are activated in models of depression. These neurons are activated by stimuli linked to disappointment or anticipation of a negative outcome, and they modulate dopamine-rich regions of the brain that control reward-seeking behavior and play a part in depressive disorders.

Researchers at the University of California, San Diego School of Medicine, along with co-investigators at Cold Spring Harbor Laboratory and Brookhaven National Laboratory, set out to investigate the cellular basis of behavioral depression by studying the synaptic activity of LHb neurons in rats.

Their study, published in the February 24 issue of the journal *Nature*, showed abnormally strong activity in the neuronal synapses of the LHb in a rat model of depression. Additionally, when these synapses were inactivated, the animals recovered from the depressive symptoms to some degree.

The research suggests that targeting the specific synapses in this part of the brain could reduce symptoms in humans with severe, chronic depression.

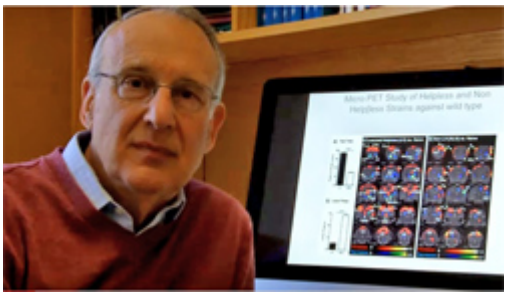
roberto Malinow, MD, PhD

"It's possible that the genes specifically expressed in these neurons could be targeted genetically or pharmacologically in order to manipulate them and reduce depression," said Roberto Malinow, MD, PhD, professor of neurosciences at the UC San Diego School of Medicine and Shiley-Marcos Endowed Chair in Alzheimer's Disease Research, who pointed out that the LHb also has the highest concentration of receptors to opiates.

The scientists utilized widely used animal models of depression called acute learned helplessness (aLH), and a strain of rats with congenital learned helplessness (cLH), produced by selective breeding of animals displaying the greatest amount of aLH. In both types, the researchers examined transmission to the LHb neurons, which receive major inputs from numerous parts of the brain involved in stress response, as well as those linked to pleasure and pain.

"The studies showed a significant correlation between increased activation of LHb neurons and an individual animal's helpless behavior – behavior that mirrors the type of inertia or helplessness often experienced in humans with depression," said Malinow. Depleting transmission by repeated electrical stimulation of LHb input nerves – using a protocol that can be effective with depressed patients – dramatically suppressed the synaptic activity, and reduced learned helplessness behavior in the rats.

"Since the communication activity in this particular part of the brain was increased in aLH and cLH rats compared to control animals, it appears that such increased activity contributes to helplessness," Malinow said. "Even without negative stimulus, the cLH rats demonstrated helplessness, or depressive-like symptoms, leading us to conclude that synapses in the lateral habenula may be genetically encoded to be abnormally active."



click on photo (above) to watch video of Co-Principal Investigator Fritz Henn of Cold Spring Harbor Laboratory discussing the study.

Contributors to the study include first author Bo Li, Center for Neural Circuits and Behavior, UC San Diego Departments of Neuroscience and Biological Sciences, and Cold Spring Harbor Laboratory; Joaquin Piriz, ChiHye Chung and Christophe D. Proulx, UC San Diego Center for Neural Circuits and Behavior; Martine Mirrione and co-principal investigator Fritz Henn, Cold Spring Harbor and Brookhaven National Laboratories; and Daniela Schulz, Brookhaven National Laboratory.

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