Manipulating a single gene defines a new pathway to anxiety

August 24 2017

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Removing a single gene from the brains of mice and zebrafish causes these animals to become more anxious than normal. Researchers from University of Utah Health show that eliminating the gene encoding Lef1

disrupts the development of certain nerve cells in the hypothalamus that affect stress and anxiety. These results are the first implication that Lef1 functions in the hypothalamus to mediate behavior, knowledge that could prove useful for diagnosing and treating human brain disorders.

"Anxiety is an essential behavior that is much more complex than we thought," says first author Yuanyuan Xie, Ph.D., who led the research in collaboration with senior author Richard Dorsky, Ph.D., professor of Neurobiology and Anatomy at U of U Health. Lef1 is a component of the Wnt signaling pathway, which has roles in animal development, physiology, and disease.

"This work is making us think about how brain structures control behavior in a different way," Xie says. The study appears in *PLOS Biology* on Aug. 24.

Humans, mice, fish, and even flies exhibit anxiety, triggering behaviors that heighten awareness. Despite its reputation, the uneasy feeling can be a good thing: in the case of zebrafish causing them to freeze in their tracks so they can hide in plain sight from predators. But being anxious at inappropriate times is counterproductive and can be a sign of unnecessary stress, a characterization that holds true not only for fish but also for people.

When Xie and Dorsky started their investigation, they had no reason to believe that Lef1 had a specific role in anxiety. Brains of fish missing the gene were relatively normal except there were cells missing from a region called the hypothalamus. This part of the brain controls many "hard-wired" behaviors such as sleep and feeding, as well as hormone release through the pituitary gland. "Before we did the experiments we had no idea that the neurons impacted by Lef1 would preferentially impact one type of behavior," says Dorsky.

Tallying the genes that were most perturbed by loss of Lef1 in this brain region revealed that over 20 were involved in mood disorders like depression and anxiety. The scientists then noticed that the fish had telltale signs consistent with these disorders. The animals were reluctant to explore their environment when placed into a new tank, preferred to remain immobile at the bottom. And they grew slowly, another condition often related to elevated stress.

Different Paths to One Behavior

Despite the fact that brain structure and complexity vary greatly from flies to humans, Lef1 appears to mediate anxiety across species. The new study shows that unexpectedly, the gene utilizes diverse mechanisms to get the job done.

Similar to zebrafish, mice in which Lef1 had been removed from the hypothalamus showed signs of anxiety, including being smaller and a reluctance to explore. They also had fewer brain cells in the region where Lef1 is normally present. However, the missing cells make Pro-melanin concentrating hormone (Pmch), a brain signal that was not perturbed in zebrafish. By contrast, zebrafish and Drosophila fruit flies lacking their versions of Lef1 are missing cells that make Corticotropin releasing hormone binding protein (Crhbp), and these cells were unaffected in mice.

These results suggested that Lef1 could regulate anxiety through two different nerve cell signals. Support for this scenario was unexpectedly found in humans, where expression of Crhbp and Pmch are extremely closely linked in the hypothalamus, indicating they may actually be present in the same cells and together act downstream of Lef1 to regulate behavior.

"When you think about genes with a conserved function you think

everything that gene does must be the same in all animals. But our study shows that that isn't necessarily true," says Dorsky.

The observation could explain how a gene that specifies a particular behavior can adapt to accommodate changes in brain circuitry that happen over evolutionary time. "Our results suggest that during evolution, the brain can innovate different ways to get to the same outcome," Dorsky explains.

The findings highlight specific sets of genes and the brain cells they affect as being involved in regulating anxiety. Future work will focus on determining whether these pathways may define a subset of human behavioral and mood disorders.

Provided by University of Utah