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Drug prevents post-traumatic stress-like symptoms in mice

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When injected into mice immediately following a traumatic event, a new drug prevents the animals from developing memory problems and increased anxiety that are indicative of post-traumatic stress disorder (PTSD).

Howard Hughes Medical Institute scientists utilized mouse studies to suggest that a receptor called Oprl1 is altered in mice with PTSD-like symptoms. They then worked with a group at the Scripps Research Institute who had previously developed the Oprl1-targeted drug to examine its effects on fear memory modulation.

The group has also shown that in humans, genetic variants of the Oprl1 gene are associated with higher risk of developing the disorder after exposure to trauma. The results, published June 5, 2013, in *Science Translational Medicine*, suggest that the new drug could have a similar preventive effect on PTSD in humans.

"PTSD is a tractable problem that can be prevented and treated if we put our mind to it," says HHMI investigator Kerry J. Ressler of the Emory University School of Medicine, who led the new work. "Bringing neuroscience and genetic approaches together provides a powerful way to understand this debilitating illness."

In humans, PTSD can be brought on by traumatic events including serious injuries or exposure to violence. The symptoms can include constant re-imagining of the traumatic event, an overall numbing to

emotions, excess anxiety, and unpredictable bouts of anger. Studies have found that military veterans–particularly those who have served directly in combat–have an especially high risk of developing PTSD. Psychotherapy and medications can help treat the symptoms of PTSD, but developing methods to prevent PTSD in at-risk individuals remains an important goal.

To uncover genes associated with PTSD in mice, Ressler's team established a series of traumatic events and tests to cause and gauge PTSD-like symptoms in the animals and differentiate between PTSD and milder learned fears. Mice that had received traumatic exposure to immobilization stress showed abnormalities days later in memory, anxiety, and distinguishing between safety and danger. The altered behaviors parallel many of the symptoms of PTSD in humans. The scientists then studied the patterns of gene expression in these mice. They homed in on one gene that was expressed in the brain and significantly turned down in the PTSD-like mice when compared to other mice.

The gene encodes the nociceptin receptor, Oprl1, which is part of a family of opioid receptors responsible for controlling the brain's response to pain processing. To test whether increased levels of Oprl1 could treat or prevent the mice's PTSD symptoms, Ressler and his colleagues used a newly developed compound from the Scripps Research Institute that activates the receptor. The drug, they showed, could be given systemically or injected directly into the brain, and administered before or shortly after the mice were immobilized. In all cases, it blocked the formation of PTSD symptoms in the animals.

Ressler then wanted to see whether Oprl1 could be linked to PTSD in humans, so looked at the gene's sequence in approximately 1,800 highly traumatized civilians, some of whom had PTSD and others who did not. One variant of Oprl1, he found, was more prevalent among those who

had the disorder. Brain scans confirmed that in those with the variant of the gene, areas of the brains associated with fear had altered patterns of fear-related activity. The findings indicate that not only might Oprl1 become dysregulated in humans following the development of PTSD, but inherited variants of the disease could increase the likelihood of someone developing the disorder to begin with.

"There are likely many, many genes that are involved in the risk for PTSD following trauma," says Ressler. "Oprl1 may be one of the many genes that contribute risk, though larger samples and replication studies are required to be certain of this."

Ressler's lab group is planning follow-up studies to examine in more detail the role of the Oprl1 receptor in humans, and test the safety of the Oprl1-targeting drug. If the drug is deemed safe and the role of Oprl1 in humans mimics that seen in mice, Ressler would move toward testing how it could be used to prevent PTSD.

"For any drug used to prevent PTSD, we would want to know who was most at-risk based on psychological and biomarker approaches," Ressler says. "We would then predict that if we gave those individuals such a drug within a few hours after trauma, it would prevent the development of PTSD pathology."

More information: "Amygdala-Dependent Fear Is Regulated by Oprl1 in Mice and Humans with PTSD," by R. Andero et al. *Science Translational Medicine*, 2013.

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