Medical Xpress

With altered brain chemistry, fear is more easily overcome

June 12 2012

Researchers at Duke University and the National Institutes of Health have found a way to calm the fears of anxious mice with a drug that alters their brain chemistry. They've also found that human genetic differences related to the same brain chemistry influence how well people cope with fear and stress.

It's an advance in understanding the brain's fear circuitry that the research team says may hold particular promise for people at risk for anxiety disorders, including those suffering post-traumatic stress disorder (PTSD).

"What is most compelling is our ability to translate first from mice to human neurobiology and then all the way out to human behavior," said Ahmad Hariri, a neurobiologist at the Duke Institute for Genome Sciences & Policy. "That kind of translation is going to define the future of psychiatry and neuroscience."

The common thread in their studies is a gene encoding an enzyme called fatty acid amide hydrolase, or FAAH. The enzyme breaks down a natural endocannabinoid chemical in the brain that acts in essentially the same way that Cannabis, aka marijuana, does (hence the name endocannabinoid).

Earlier studies had suggested that blocking the FAAH enzyme could decrease fear and anxiety by increasing endocannabinoids. (That's consistent with the decreased anxiety some experience after smoking

marijuana.) In 2009, Hariri's lab found that a common variant in the human FAAH gene leads to decreased enzyme function with affects on the brain's circuitry for processing fear and anxiety.

In the new study, Andrew Holmes' group at the National Institute on Alcoholism and Alcohol Abuse tested the effects of a drug that blocks FAAH activity in fear-prone mice that had also been trained to be fearful through experiences in which they were delivered foot shocks.

Tests for the ability of those mice to get over their bad experiences found that the drug allowed a faster recovery from fear thanks to higher brain endocannabinoid levels. More specifically, the researchers showed that those drug effects traced to the amygdala, a small area of the brain that serves as a critical hub for fear processing and learning.

To test for the human relevance of the findings, Hariri's group went back to the genetic variant they had studied earlier in a group of middle-aged adults. They showed study participants a series of pictures depicting threatening faces while they monitored the activity of their amygdalas using functional magnetic resonance imaging (fMRI) scans. They then looked for how the genetic variant affected this activity.

While the activity of the amygdala in all participants decreased over repeated exposures to the pictures, people who carried the version of the FAAH gene associated with lower enzyme function and higher endocannabinoid levels showed a greater decrease in activity. Hariri says that suggests that those individuals may be better able to control and regulate their fear response.

Further confirmation came from an analysis led by Duke's Avshalom Caspi and Terrie Moffitt of 1,000 individuals in the Dunedin Study (http://dunedinstudy.otago.ac.nz/), who have been under careful observation since their birth in the 1970s in New Zealand. Consistent

with the mouse and brain imaging studies, those New Zealanders carrying the lower-expressing version of the FAAH gene were found to be more likely to keep their cool under stress.

"This study in mice reveals how a drug that boosts one of the brain's naturally occurring endocannaboids enables fear extinction, a process that forms the basis of exposure therapy for PTSD," Holmes said. "It also shows how human gene variation in the same chemical pathways modulates the amygdala's processing of threats and predicts how well people cope with stress."

Studies are now needed to further explore both the connections between FAAH variation and PTSD risk as well as the potential of FAAH inhibition as a novel therapy for fear-related disorders, the researchers say.

More information: "Convergent Translational Evidence of a Role for Anandamide in Amygdala-Mediated Fear Extinction, Threat Processing and Stress-Reactivity," O Gunduz-Cinar, KP MacPherson et al. *Molecular Psychiatry*, June 12th. doi:10.1038/mp.2012.72

Provided by Duke University