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Drug Prevents Post-Traumatic Stress Syndrome, Study Suggests

Post-traumatic stress syndrome -- when a severely stressful event triggers exaggerated and chronic fear -- affects nearly 8 million people in the United States and is hard to treat. In a preclinical study, Northwestern Medicine scientists have for the first time identified the molecular cause of the debilitating condition and prevented it from occurring by injecting calming drugs into the brain within five hours of a traumatic event.

Northwestern researchers discovered the brain becomes overly stimulated after a traumatic event causes an ongoing, frenzied interaction between two brain proteins long after they should have disengaged.

"It's like they keep dancing even after the music stops," explained Principal Investigator Jelena Radulovic, Associate Professor of Psychiatry and Behavioral Sciences and Dunbar Scholar at Northwestern University Feinberg School of Medicine. When newly developed research drugs MPEP and MTEP were injected into the hippocampus, the calming drugs ended "the dance."

"We were able to stop the development of exaggerated fear with a simple, single drug treatment and found the window of time we have to intervene," Radulovic said. "Five hours is a huge window to prevent this serious disorder." Past studies have tried to treat the extreme fear responses, after they have already developed, she noted.

The study, conducted with mice, was published Dec. 1 in the journal Biological Psychiatry.

An exaggerated fear disorder can be triggered by combat, an earthquake, a tsunami, rape or any traumatic psychological or physical event.

"People with this syndrome feel danger in everything that surrounds them," Radulovic said. "They are permanently alert and aroused because they expect something bad to happen. They have insomnia; their social and family bonds are severed or strained. They avoid many situations because they are afraid something bad will happen. Even the smallest cues that resemble the traumatic event will trigger a full-blown panic attack."

In a panic attack, a person's heart rate shoots up, they may gasp for breath, sweat profusely and have a feeling of impending death.

Many people bounce back to normal functioning after stressful or dangerous situations have passed. Others may develop an acute stress disorder that goes away after a short period of time. But some go on to develop post-traumatic stress syndrome, which can appear after a time lag.

The stage is set for post-traumatic stress disorder after a stressful event causes a natural flood of glutamate, a neurotransmitter that excites the neurons. The excess glutamate dissipates after 30 minutes, but the neurons remain frenzied. The reason is the glutamate interacts with a second protein (Homer1a), which continues to stimulate the glutamate receptor, even when glutamate is gone.

For the study, Northwestern scientists first subjected mice to a one-hour immobilization, which is distressing to them but not painful. Next, the mice explored the inside of a box and, after they perceived it as safe, received a brief electric shock. Usually after a brief shock in the box, the animals develop normal fear conditioning. If they are returned to the box, they will freeze in fear about 50 percent of the time. However, after the second stressful

experience, these mice froze 80 to 90 percent of the time.

The animals' exaggerated chronic fear response continued for at least one month and resembles post-traumatic stress disorder in humans, Radulovic said.

For the second part of the study, Natalie Tronson, a postdoctoral fellow in Radulovic's Dunbar Laboratory for Research on Memory and Fear, and Radulovic repeated the two stressful experiences with the mice but then injected them with MPEP and MTEP five hours after the immobilization. This time the mice did not develop the exaggerated fear response and froze for only 50 percent of the time.

"The mice's fear responses were completely normal," Radulovic said. "Their memories of the stressful event didn't trigger the extreme responses anymore. This means we could have a prevention approach for humans exposed to acute, severe stressful events."

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