For those at high risk, PTSD may be treatable before traumatic events even occur

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Credit: Nate Edwards/BYU Photo

When people experience trauma, medication can help prevent or reduce post-traumatic stress disorder, softening overly strong memories that cause debilitating flashbacks and nightmares. But this treatment works

only if the pills are taken promptly after a traumatic experience.

New Brigham Young University research published in the *International Journal of Molecular Sciences* shows the potential for an improved method that could block PTSD-strength memories from forming to begin with.

"We were really curious about whether some of those drugs used to reverse PTSD could be given to people we know have high risks—such as first responders or people in the military—before they experience stress, to prevent some of the cellular-level brain changes that are damaging in PTSD," said BYU neuroscience professor Jeff Edwards, who led the study.

Edwards first became interested in studying PTSD when his barber, a Vietnam War veteran, described going to a war movie and finding himself standing in the theater shouting, experiencing combat all over again.

To see if PTSD pretreatment is worth pursuing in human trials, Edwards and his team used rats for a proof of concept. The researchers first injected some of the rats with propranolol and mifepristone, the drugs commonly used to treat PTSD retroactively. They then generated PTSD-inducing chronic and acute stress by exposing the rats to constant light for two weeks and subjecting them to "social defeat," periodically introducing a dominant rat into the space to frighten the rat subjects.

A week later, they tested the rats for anxious behavior and then examined the amygdala and hippocampus, the areas associated with emotion and memory, in each rat's brain. They were looking for how stress affected the degree of long-term potentiation (LTP)—the strengthening of synapses or junctions between neurons that facilitates memory formation. The higher the LTP, the stronger the memory;

excessively high LTP would indicate a PTSD-like effect.

As expected, rats undergoing stress without drug pretreatment showed huge increases in LTP, a 30–40% enhancement. But the rats treated with the drugs before undergoing social defeat had the same levels of LTP as the control group rats that didn't undergo any stress.

"The drugs brought the brain back to normal levels, how it should be working in memory formation, eliminating some of those maladaptive memories that create overly strong recall," Edwards said.

The scientists also found that the pretreated rats' stress receptors were normal after experiencing trauma, while the stress receptors of the rats that didn't receive treatment were 80% less functional.

"Preventative treatment strategies like this are often much more effective," said Eric Winzenried, who worked on the project as a BYU undergraduate and is now a neuroscience Ph.D. student at Washington State University. "You can think of the adage, 'An ounce of prevention is worth a pound of cure.' Although our work is very preliminary and in rodents, it is a piece in the puzzle that we hope will lead to better treatments for the prevention of PTSD in high-risk individuals."

The next steps before a human trial include developing a more fine-grained understanding of how the medications work to reduce PTSD-like effects in the rats. For example, the researchers may try giving the rats either propranolol or mifepristone instead of both, to see if just one will suffice.

As they work toward broader applications, doing proof-of-concept studies is giving BYU students valuable research experiences. "At BYU, I was surrounded by faculty members and classmates who pushed and inspired me to fulfill my potential as a scientist," said Anna Everett, who

participated in the research as an undergraduate and is now pursuing a neuroscience Ph.D. at Harvard.

More information: Eric T. Winzenried et al, Effects of a True Prophylactic Treatment on Hippocampal and Amygdala Synaptic Plasticity and Gene Expression in a Rodent Chronic Stress Model of Social Defeat, *International Journal of Molecular Sciences* (2023). DOI: 10.3390/ijms241311193

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