

Forget It! A Biochemical Pathway For Blocking Your Worst Fears?

ScienceDaily (Mar. 26, 2009) — A receptor for glutamate, the most prominent neurotransmitter in the brain, plays a key role in the process of "unlearning," report researchers at the Salk Institute for Biological Studies.

Their findings, published in the current issue of the *Journal of Neuroscience*, could eventually help scientists develop new drug therapies to treat a variety of disorders, including phobias and anxiety disorders, particularly post-traumatic stress disorder.

"Most studies focus on 'learning,' but the 'unlearning' process is probably just as important and much less understood," says Stephen F. Heinemann, Ph.D., a professor in the Molecular Neurobiology Laboratory, who led the study. "Most people agree that failure to 'unlearn' is a hallmark of post-traumatic stress disorders and if we had a drug that affects this gene it could help soldiers coming back from the war to 'unlearn' their fear memories."

Post-traumatic stress disorder or PTSD is an anxiety disorder that can develop after exposure to a terrifying event or ordeal in which grave physical harm occurred or was threatened. PTSD is affecting approximately 5.2 million Americans, according to the National Institute of Health. As many as one in eight returning soldiers suffer from PTSD.

But you don't have to be a combat soldier to develop anxiety disorders such as PTSD. Any bad experience in daily life is a learning experience that can result in anxiety disorders. If traumatic memories persist inappropriately, sensory cues, sometimes not even recognized consciously, trigger recall of the distressing memories and the associated stress and fear.

As a way of modeling anxiety disorders in humans, researchers train mice to fear a tone by coupling it with a foot shock. If this fear conditioning is followed by repeated exposure to the tone without aversive consequences, the fear will subside, a behavioral change called fear extinction or inhibitory learning.

Heinemann and his team were particularly interested in whether mGluR5, short for metabotropic glutamate receptor 5, which had been shown to be involved in several forms of behavioral learning, also plays a role in inhibitory learning. "Inhibitory learning is thought to be a parallel learning mechanism that requires the



Researchers have found a receptor for glutamate that plays a key role in the process of "unlearning" -- a finding that could eventually help scientists develop new drug therapies to treat a variety of disorders, including phobias and anxiety disorders. (Credit: iStockphoto/Diane Diederich)

acquisition of new information as well as the suppression of previously acquired experiences to be able to adapt to novel situations or environments," says Heinemann.

When senior research associate and first author Jian Xu, Ph.D., put mice lacking the gene for mGluR5 through the fear extinction-drill, they were unable to shake off their fear of the now harmless tone. "We could train the mice to be afraid of the tone but they were unable to erase the association between the tone and the negative experience," he says.

In the second series of experiments, Xu tested whether deleting mGluR5 also affected animals' ability to learn new spatial information. He first trained mice to find a hidden platform placed in a fixed location in the water maze. Although it took mutant mice slightly longer than control animals to remember the position of the submerged platform, after several days of training the mutants finally got the hang of it and were able to find it almost as quickly as the control animals.

Xu then moved the platform to a different location in the water maze and re-trained the animals. He observed that normal animals quickly adjusted their searching strategy once they realized that the platform had been moved to a different spot. The mice lacking mGluR5, however, just couldn't get it into their heads that the platform was no longer there and kept coming back to the original location. It took them several more trials until they finally gave up searching in the old location.

"Mice without mGluR5 had severe deficits in tasks that required them to 'unlearn' what they had just learned," explains Xu. "We believe that the same mechanism is perturbed in PTSD and that mGluR could provide a potential target for therapeutic intervention."

In addition to Xu and Heinemann, postdoctoral researchers Yongling Zhu, Ph.D., and Anis Contractor, Ph.D., contributed to the research.

Journal reference:

1. Jian Xu, Yongling Zhu, Anis Contractor, and Stephen F. Heinemann. **mGluR5 Has a Critical Role in Inhibitory Learning**. *Journal of Neuroscience*, 2009; 29 (12): 3676 DOI: [10.1523/JNEUROSCI.5716-08.2009](https://doi.org/10.1523/JNEUROSCI.5716-08.2009)

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