Drug substitutes for training in rats, inducing a memory of safety

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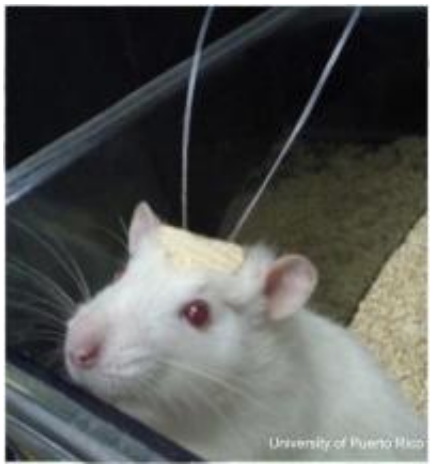

A laboratory rat being injected with brain-derived neurotrophic factor (BDNF) directly into the brain. BDNF created a memory of safety in rats that were afraid. Credit: Dr. Gregory Quirk, University of Puerto Rico

Researchers have found a way to pharmacologically induce a memory of safety in the brain of rats, mimicking the effect of training. The finding suggests possibilities for new treatments for individuals suffering from anxiety disorders.

Rats normally freeze when they hear a tone they have been conditioned to associate with an electric shock. The reaction can be extinguished by repeatedly exposing the rats to the tone with no shock. In this work, administering a protein directly into the brain of rats achieved the same

effect as extinction training. The protein, brain-derived neurotrophic factor or BDNF, is one of a class of proteins that support the growth and survival of neurons.

Prior work has shown that extinction training does not erase a previously conditioned fear memory, but creates a new memory associating the tone with safety. "The surprising finding here is that the drug substituted for extinction training, suggesting that it induced such a memory," said Dr. Gregory Quirk at the University of Puerto Rico School of Medicine, who led the investigation with support from the National Institute of Mental Health. The work is reported in the June 4 issue of *Science*.

Memory formation involves changes in the connections, or synapses, between neurons, a process known as synaptic plasticity. One brain structure critical for extinction memory in rats is the infralimbic prefrontal cortex (ILC). Drugs that block synaptic plasticity impair the formation of extinction memory when injected into the ILC, causing rats to continue freezing at high levels after extinction training.

BDNF, on the other hand, permits a learning experience to increase the size and strength of synaptic contacts between neurons. Previous work from other groups has implicated BDNF in extinction learning. In this study, after rats were conditioned to fear a tone by pairing it with a footshock, BDNF was infused directly into the ILC. The next day, BDNF-infused rats showed little freezing to the tone, as if they had received extinction training.

Experiments showed that BDNF-induced extinction did not erase the original fear memory. Training to reinstate the tone-shock association was just as effective with the rats receiving BDNF as those without. Also, the effect of BDNF was specific to extinction. It did not reduce general anxiety or change the animals' tendency to move around.

The researchers also found that rats that were naturally deficient in BDNF were more likely to do poorly in extinction trials. These rats were deficient in BDNF in the hippocampus, a brain structure that plays an important role in memory and extinction, and which has connections to the ILC. Failure to extinguish fear is thought to contribute to anxiety disorders, such as post-traumatic stress disorder (PTSD). People with PTSD have a smaller than normal hippocampus and ILC.

"Many lines of evidence implicate BDNF in mental disorders," said NIMH Director Dr. Thomas Insel. "This work supports the idea that medications could be developed to augment the effects of BDNF, providing opportunities for pharmaceutical treatment of post-traumatic stress disorder and other anxiety disorders." The focus now is to look for ways to augment BDNF's actions in the brain, which might include anti-depressant medications and even exercise.

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