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Learned safety cheers depressed mice: An animal model of behavioral intervention for depression

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A new animal model has provided insight into the cellular and molecular mechanisms associated with behavioral therapy for depression. The study, published by Cell Press in the October 9th issue of *Neuron,* may provide a good model system for testing cellular and molecular interactions between antidepressive medications and behavioral treatments for depression.

Organisms ranging from simple invertebrates to mammals have evolved mechanisms for instinctive and learned fear that are critical for survival. However, in humans, pathological forms of learned fear can contribute to anxiety disorders, posttraumatic stress, and depression. "The fact that learned fear can be associated with psychopathologies in humans suggests that this form of learning is not always appropriate and that effective inhibitory constraints are likely to exist," explains Eric Kandel from Columbia University.

Previous research investigating how learned fear is processed in the brain has made use of a conditioned inhibition learning paradigm wherein an animal is conditioned to associate a target signal with protection from an impending aversive event, resulting in a reduction of conditioned fear. This process, where an animal learns to take advantage of sources of security in the environment, is thought to represent a form of "learned safety."

Daniela Pollak in the Kandel lab was interested in attempting to characterize some of the behavioral consequences of learned safety as well as exploring the phenomenon at the molecular level. She observed that learned safety reduced depression-like behavior in mice in a manner that was comparable to that seen with pharmacological antidepressants. Consistent with the behavioral antidepressant effects, learned safety also shared neurobiological hallmarks associated with other antidepressant therapies. Specifically, learned safety promotes the survival of newborn nerve cells and expression of critical growth factors in the hippocampus.

The researchers went on to search for differentially regulated genes in the amygdala of safety- and fear-conditioned mice. The amygdala is a brain region associated with emotional symptoms that are a hallmark of depression. Learned safety led to decreased expression of genes involved in dopamine and substance P signaling, but not serotonin signaling. This is significant because serotonin receptors are a major target of popular antidepressant medications.

"We propose a model in which the stress-reducing and antidepressant effects of learned safety are mediated through the interaction of (at least) two different neurotransmitter systems. Our findings suggest that learned safety is an animal model of a behavioral antidepressant that shares some of the neuronal modifications typical of pharmacological antidepressant, but is mediated by different molecular pathways," offers Kandel.

Source: Cell Press