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What does chronic stress in adolescence mean at the molecular level?

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Chronic stress has a more powerful effect on the brain during adolescence than in adulthood and now there's proof at the molecular level, according to findings published in *Neuron* by University at Buffalo researchers.

"We have identified a causal link between molecules and behaviors involved in stress responses," says Zhen Yan, PhD, a professor in the Department of Physiology and Biophysics in the UB School of Medicine and Biomedical Sciences. "It's the first time that the loss of glutamate receptor has been causally linked to the negative effects of chronic or repeated stress."

The UB research bolsters the emerging understanding among neuroscientists that the glutamate system is a key player in mental illness and, thus, is critical to understanding how to better treat disorders like depression, anxiety and schizophrenia.

Yan and her colleagues wanted to better understand the molecular mechanisms of stress, about which little is known. She and her colleagues had previously found that acute stress helps sharpen memory (see related story from 2009). Now they have found that chronic stress has the opposite effect.

The UB research was conducted on male rats at an age that corresponds to adolescence in humans, a period when the brain is highly sensitive to stress. This is especially true of the prefrontal cortex, which doesn't fully

mature until age 25 in humans and which undergoes dramatic change during adolescence. The prefrontal cortex is referred to as the "CEO" of the brain, controlling working memory, decision-making and attention.

In response to repeated stress, Yan and her colleagues found there was a loss of glutamate receptor expression and function in the prefrontal cortex. That loss resulted in a significant impairment in the ability of the adolescent animals to remember and recognize objects they had previously seen. The same cognitive deficit was not seen in the similarly stressed adults.

"Because dysfunction in the prefrontal cortex has been implicated in stress-related mental illness, this research identifying how stress affects prefrontal cortical functions will help further unravel how and why mental illnesses occur and how to treat them," says Yan.

In the same paper, the researchers report that by disrupting the enzymes that trigger loss of glutamate receptor expression, they were able to prevent the cognitive impairment induced by repeated stress exposure.

As a result, the UB researchers have discovered that there may be a way to prevent the detrimental effects of chronic stress.

Many antipsychotic drugs currently on the market do somehow affect the glutamate system. Yan and her UB colleagues recently published research in Molecular Pharmacology, showing how one of the newer antipsychotics, lurasidone, (trade name Latuda) does just that. But, she notes, many of these drugs also affect other important neurotransmitter systems as well.

"If, based on this research, we can begin to target the glutamate system in a more specific and effective way, we might be able to develop better drugs to treat serious mental illness," she says.

The research is especially significant because with some mental disorders, such as schizophrenia, onset typically occurs in late adolescence.

"While there have been many behavioral studies about stress, understanding stress at a molecular level is key to developing strategies to prevent stress-induced behavioral deficits," says Yan. "In the end, it has to be boiled down to molecules. Without knowing why something happens at a molecular level, you cannot do anything about it."

More information: Yuen et al.: "Repeated Stress Causes Cognitive Impairment by Suppressing Glutamate Receptor Expression and Function in Prefrontal Cortex." DOI:10.1016/j.neuron.2011.12.033

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