Tolerance to inhalants may be caused by changes in gene expression

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Changes in the expression of genes may be the reason why people who abuse inhalants, such as spray paint or glue, quickly develop a tolerance, biologists at The University of Texas at Austin have discovered.

The team, led by graduate student Yan Wang, used the fruit fly Drosophila melanogaster as a model system to determine how the nervous system becomes tolerant to sedation with organic solvent inhalants.

The team's work appears in the October 16 issue of Public Library of Science-Biology.

"Drug tolerance causes the user to consume more of the drug, speeding them down the path of addiction," said Nigel Atkinson, an associate professor of neurobiology who supervised the research.

This is the first study to show that a single drug experience alters the response of an animal to future doses by epigenetically modifying a single gene.

The research lays the groundwork for understanding mechanisms of inhalant addiction in humans, and it is hoped, developing methods of treatment and recovery. Because the effects of organic solvent inhalants and alcohol on animals are similar, this work may also be relevant to understanding the response of the brain to alcohol.

When fruit flies are sedated with an organic solvent, the expression of the slo K+ channel gene increases. Increased expression of the gene enables the fruit flies to recover faster from sedation. This gene is very similar to the human slo gene.

Wang and colleagues sedated fruit flies with the organic solvent benzyl alcohol, then documented changes in chromosomal structures called histones. Histones are positively charged protein structures that bind to negatively charged DNA. They organize and control access to the DNA.

Benzyl alcohol sedation made the charge of the histone more negative, "relaxing the grip" of the DNA to the histones in a part of the slo gene that controls its expression.

When the chromatin is in a relaxed state, gene transcription occurs more frequently.

The researchers predict that increased expression of the slo channels, through epigenetic modifications to the histones, helped neurons recover from sedation and resist the effects of the drug, increasing tolerance.

"While the fruit fly seems very different from us, the cells of its nervous system are remarkably similar to ours and can be used to understand how drugs change our brains," Atkinson said.

Source: University of Texas at Austin