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Cancer drug enhances long-term memory

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A drug used to treat cancer has been shown to enhance long-term memory and strengthen neural connections in the brain, according to a new study by UC Irvine scientists.

In the study with mice, scientists found that histone deacetylase (HDAC) inhibitors – currently used in clinical trials to attack cancerous tumors – relaxes the protein structure that organizes and compacts genomic DNA, allowing for easier activation of genes involved in memory storage. This finding suggests that HDAC inhibitors could boost memory in humans and – because of the way they work – be therapeutic for people with Alzheimer's and Huntington's diseases and Rubenstein-Taybi syndrome.

"We have demonstrated for the first time that HDAC inhibitors applied directly to the hippocampus enhance memory and synaptic plasticity in the brain, and we now know a molecular mechanism through which these enhancements occur," said Marcelo Wood, assistant professor in the Department of Neurobiology and Behavior at UCI and an author of the study.

This study appears June 6 in the *Journal of Neuroscience*.

A protein complex called chromatin causes genomic DNA to compress much like a telephone cord shortens as it coils. When chromatin loosens, genes associated with memory can activate more easily. Previous studies have shown that the protein CBP causes chromatin to relax, thus facilitating gene activation required for memory formation. The enzymes that reverse this process, or make the chromatin tighter, are

known as HDACs. UCI scientists found in this study that HDAC inhibitors loosen chromatin and lead to stronger memory formation.

“This is a fundamental aspect of molecular biology, and it is fascinating that it can impact memory, cancer and neurodegeneration – and potentially other conditions such as drug addiction and other psychiatric disorders,” said Wood, also a fellow of the UCI Center for the Neurobiology of Learning and Memory.

Wood and his colleagues placed mice in a chamber and gave them mild electric shocks, similar to static electricity shocks that humans can get when they walk across a rug and touch a door knob. Afterward, scientists injected HDAC inhibitors into the brains of mice, targeting the hippocampus, a region involved in short-term and long-term memory. A day later, the scientists returned the mice to the chamber to see how well they remembered the place in which they received the shock. Mice treated with HDAC inhibitors froze in place significantly longer than those that did not receive the drug, indicating that the treated mice formed stronger memories of the chamber than the untreated mice. The scientists also examined brain tissue and found that neural connections in the hippocampus were stronger in the samples treated with HDAC inhibitors.

“After an event, a critical window exists when memory consolidation is occurring. During that time, genes associated with memory need to be turned on for certain types of long-term memory to be formed,” Wood said. “For the HDAC inhibitor to enhance memory, we need to administer the drug during this critical period when gene expression is required.”

The protein CBP must be present for HDAC inhibitors to improve memory, Wood and his colleagues discovered. Tested in mice genetically engineered without CBP, the HDAC inhibitors did not

improve memory. When CBP is blocked in humans, it can lead to neurodegeneration associated with Huntington's disease and cognitive deficits in Rubenstein-Taybi syndrome. HDAC inhibitors may help overcome that blockage and lead to better neural function in people with those disorders – and perhaps improve memory as well.

Source: University of California - Irvine