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Drug triggers body's mechanism to reverse aging effect on memory process

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A drug made to enhance memory appears to trigger a natural mechanism in the brain that fully reverses age-related memory loss, even after the drug itself has left the body, according to researchers at UC Irvine.

Professors Christine Gall and Gary Lynch, along with Associate Researcher Julie Lauterborn, were among a group of scientists who conducted studies on rats with a class of drugs known as ampakines. Ampakines were developed in the early 1990s by UC researchers, including Lynch, to treat age-related memory impairment and may be useful for treating a number of central nervous system disorders, such as Alzheimer's disease and schizophrenia. In this study, the researchers showed that ampakine drugs continue to reverse the effects of aging on a brain mechanism thought to underlie learning and memory even after they are no longer in the body. They do so by boosting the production of a naturally occurring protein in the brain necessary for long-term memory formation.

The study appears in the August issue of the *Journal of Neurophysiology*.

"This is a significant discovery," said Gall, professor of anatomy and neurobiology. "Our results indicate the exciting possibility that ampakines could be used to treat learning and memory loss associated with normal aging."

The researchers treated two groups of middle-aged rats twice a day for four days with either a solution that contained ampakines or one that did

not. They then studied the hippocampus region of the rats' brains, an area critical for memory and learning. They found that in the ampakine-treated rats, there was a significant increase in the production of brain-derived neurotrophic factor (BDNF), a protein known to play a key role in memory formation. They also found an increase in long-term potentiation (LTP), the process by which the connection between the brain cells is enhanced and memory is encoded. This enhancement is responsible for long-term cognitive function, higher learning and the ability to reason. With age, deficits in LTP emerge, and learning and memory loss occurs.

Significantly, restoration of LTP was found in the middle-aged rats' brains even after the ampakines had been cleared from the animals' bodies. The drug used in the injections has a half-life of only 15 minutes; the increase in LTP was seen in the rats' brains more than 18 hours later. According to the researchers, this study suggests that pharmaceutical products based on ampakines can be developed that do not need to be in the system at all times in order to be effective. Most drugs used to deal with central nervous system disorders, such as Parkinson's disease, are only effective when they are in the body. Further studies will be needed to determine exactly how long the effect on LTP will be maintained after the ampakines leave the system.

The lingering presence of LTP also appears to contribute to BDNF remaining in the body, researchers said. "Ampakines work in two important ways to improve learning and memory," Lauterborn said. "They directly stimulate the connection between nerve cells, which has an immediate effect of boosting LTP. But they also increase the presence of this important protein, BDNF, that can stay in the body and keep boosting memory after the drug has worn off."

Source: University of California - Irvine