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Cut out the (estrogen) middleman

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Estrogen seems to act like a middleman in its positive effect on the brain, raising the possibility that future drugs may bypass the carcinogenic hormone altogether while reaping its benefits.

A split-personality chemical, estrogen is thought to protect neural circuits and boost learning and memory, while at the same time increasing cancer risk when taken in high doses.

In a study published online today in the Proceedings of the National Academy of Sciences (*PNAS*), neuroscientists at USC and the Western University of Health Sciences show that estrogen sometimes acts through another chemical.

Their experiments on mice verified that the hormone stimulates parts of the brain dedicated to learning and memory.

"We show very clearly that it does activate the same machinery that is activated during learning and memory," said Michel Baudry, professor of neurobiology at the USC College of Letters, Arts and Sciences.

But the researchers also found that estrogen acts through calpain, a protein considered crucial to learning and memory since a seminal paper in 1984 by Baudry and Gary Lynch of the University of California, Irvine on the biochemistry of memory.

Baudry is senior co-author on the PNAS study, which implies that the hormonal description of estrogen needs revisiting.

Estrogen acting through calpain does not work as a slowly diffusing hormone, Baudry said, but as a neurotransmitter with a more powerful and nearly immediate effect on the brain.

He compared estrogen to adrenalin, a substance that acts like a hormone in most of the body but as a neurotransmitter in the brain.

"It's not a hormonal effect. It's a synaptic modulator. It completely changes the way we look at estrogen in the brain," Baudry said.

That change may lead to better drugs against Alzheimer's and other neurodegenerative diseases, according to USC graduate student and lead author Sohila Zadran.

"Estrogen is critically involved in learning and memory," she said, and the PNAS study shows that its effects "critically involve calpain."

In the future, drug developers may choose to target calpain directly, possibly avoiding the risks associated with hormone therapy.

Such a strategy would not have been possible if Baudry's group had not clarified estrogen's mechanism of action.

"If you don't understand the mechanism, it really makes it difficult to go after a problem," Zadran said.

Source: University of Southern California (news : web)