Improved estrogen reception may sharpen fuzzy memory

July 29 2008

Estrogen treatments may sharpen mental performance in women with certain medical conditions, but University of Florida researchers suggest that recharging a naturally occurring estrogen receptor in the brain may also clear cognitive cobwebs.

The discovery suggests that drugs can be developed to offset "senior moments" related to low estrogen levels, as well as to protect against neurological diseases, all while avoiding the problems associated with adding estrogen to the body.

Writing online in *Molecular Therapy* in July, scientists with UF's McKnight Brain Institute describe how they improved thought processes in female mice bred with the inability to produce estrogen receptor-alpha, a protein apparently necessary for healthy learning and memory.

"We were able to restore function in these animals, not by dosing them with estrogen, but by enabling them to use the estrogen that was naturally present in their bodies," said Tom Foster, Ph.D., the Evelyn F. McKnight chair for brain research in memory loss at the UF College of Medicine. "We discovered that you can affect the estrogen receptor directly in the hippocampus, right where it's needed to address memory and spatial learning."

Changes in the estrogen receptor have been associated with age-related memory deficits and an increased incidence of Alzheimer's disease among women. In addition, previous studies have shown estrogen

replacement may improve cognition in postmenopausal women and younger women with low estrogen levels. Estrogen also appears to protect against Alzheimer's disease and dementia.

The downside is that estrogen is a powerful hormone that has far-reaching effects throughout the body. It has been associated with a slight increase in women's risk for breast cancer, heart disease in patients with existing cardiovascular problems, and stroke.

"Estrogen may act as a growth agent for cancer, but in the brain, it appears to maintain health and counteract stress," Foster said. "We wanted to come back and enhance the signaling pathway that makes estrogen functional. We used a gene therapy technique that enables us to target the brain, but ultimately there could be a pharmaceutical that enhances the signaling pathway solely in the brain."

The mice had unusually low levels of estrogen because their ovaries were removed at an early age. However, scientists were still able to rescue learning ability by delivering the correct gene to produce estrogen receptor-alpha directly to the hippocampus.

Mice that lacked the estrogen receptor showed poor ability to locate a platform hidden in a small swimming tank over a training period of several days. After receiving the gene, the mice learned to locate the platform in two days of training.

"This research shows that when the estrogen receptor-alpha is restored to adult mice that have been missing it their entire lives, it is still possible to enhance memory and learning," said John H. Morrison, Ph.D., dean of basic sciences and the Graduate School of Biological Sciences at Mount Sinai School of Medicine, who did not participate in the research. "This is good news for moving forward to develop clinical interventions and therapeutics because it appears critical damage was not done to brain

circuitry during early development. There has also been debate about which of at least two estrogen receptors is key to synaptic health. Clearly estrogen receptor-alpha plays a critically important role in hippocampal organization and function."

Recordings made from the brain tissue of treated mice showed signals were strongly communicated across the gaps, or synapses, between hippocampal cells, similar to what would happen with estrogen replacement.

"Investigating the impact of genetically replacing the estrogen receptor at the cellular, synaptic and behavioral levels is a scientific tour de force which provides a strong foundation for the role of estrogen receptor alpha in mediating estrogen action in the hippocampus to restore select types of memory function," said Roberta Diaz Brinton, Ph.D., a professor of pharmacology and pharmaceutical sciences and biomedical engineering at the University of Southern California, who was not involved in the study. "From a technology perspective, their technique to transfect the estrogen receptor is an exciting advance for researching steroid receptors in the brain."

Studying the effects of increasing the estrogen receptor in other brain regions may shed additional light on memory processes.

"The research brings up the idea that local activation of non-nuclear estrogen receptor-alpha is important for regulating memory processes in the hippocampus," said Teresa A. Milner, Ph.D., a professor of neuroscience at Weill Cornell Medical College, who also was also not involved in the research.

Source: University of Florida