Estrogen and stroke risk

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Eighteen years ago this month the National Institutes of Health (NIH) announced that it would sponsor a landmark study to examine women and cardiovascular disease. Known as the Women's Health Initiative (WHI), the study enrolled more than 161,000 women. By 2004 however, the government had ended two arms of the study involving estrogen after researchers found it posed a small but detrimental risk for stroke to postmenopausal women taking the hormone. The findings caught many members of the scientific community by surprise as estrogen had previously been shown to protect the brain from stroke in animal models.

Stroke, also known as a brain attack, is America's third leading cause of death. It typically occurs when blood flow to the brain is blocked, usually due to a clogged artery. When a stroke occurs, brain damage can result, especially in the area known as the hippocampus, thought to be the site for memory, memory loss, and learning. Despite the possible link between estrogen and stroke many women continue to take the hormone to manage their menopausal symptoms.

Does Estrogen Replacement Need to Occur Before Menopause to Protect the Brain?

Researchers at the Medical College of Georgia (MCG), along with collaborators at the North China Coal Medical University in Tangshan, China, and the University of Texas Health Sciences Center in San Antonio, have taken the understanding between the hormone and the risk, and advanced scientific understanding. Their new study, using

animals, finds that (1) estrogen clearly and strongly protects the hippocampus after stroke, thereby reducing some aspects of stroke-related brain damage; (2) that the hippocampus region of the brain becomes hypersensitive after a stroke if it has gone without sufficient levels of estrogen for long periods of time (and this study is the first to observe this transformation); (3) that long periods of low estrogen makes the hippocampus insensitive to estrogen protective effects, though the tissues of the uterus retain their sensitivity to estrogen; and (4) estrogen significantly inhibits activation of a key membrane enzyme - NADPH oxidase, which produces reactive free radical molecules that cause brain damage - following stroke.

The study provides support for the theory that there may be a "critical period" for beneficial protective effect of estrogen on the brain - e.g. that of estrogen replacement may need to be initiated prior to or at the time of menopause if estrogen is to protect the brain. Additional studies will need to confirm the findings.

The study was conducted by Darrell W. Brann, Quan-Guang Zhang, Limor Raz and Dong Han of the Institute of Molecular Medicine and Genetics, Medical College of Georgia, Augusta; Ratna Vadlamudi of the University of Texas Health Sciences Center in San Antonio, and Ruimin Wang and Fang Yang, of the Research Center for Molecular Biology, North China Coal Medical University, Tangshan. Dr. Brann presented an overview of the team's findings at the American Physiological Society (APS) conference Sex and Gender this summer. The study's findings have been accepted and been published in the November 4, 2009 online edition of the *Journal of Neuroscience* (http://www.jneurosci.org/). The article is entitled "Estrogen Attenuates Ischemic Oxidative damage via an ERα-Mediated Inhibition of NADPH Oxidase Activation."

Methodology and Findings

E2, or 17β-estradiol, is a specific form of estrogen. It is unclear how it is used to protect the brain in general or the hippocampus in particular. Rats whose ovaries had been removed were used for the study and received either placebo or 17β-estradiol after the ovaries were removed in an attempt to mimic the progression of estrogen loss during menopause.

The animals were randomly assigned to one of four groups. Group 1 experienced only sham surgery and no stroke or estrogen (sham). Group 2 was induced with stroke and immediately received a faux drug (placebo). Group 3 animals were treated with 17β-estradiol for one week after being ovariectomized and then stroke was induced. Group 4 rats received either estrogen or placebo ten weeks after being ovariectomized and one week later stroke was induced.

Samples were taken from the rats and examined. Statistical analyses were also performed. Afterwards the researchers found:

- That since there was no stroke in group 1, there was little to no free radical production in the brain.
- In group 2, there was a strong induction of the free radical superoxide, produced by the enzyme, NADPH oxidase in the hippocampus following stroke.
- In Group 3, estrogen was found to strongly block the NADPH oxidase-induced production of superoxide, and it protected the brain and reduced oxidative damage to it.
- In group 4 animals, which had been deprived of estrogen for a prolonged period similar to the situation that occurs after menopause, the protective effect of estrogen on the brain was

completely lost. It no longer blocked NADPH oxidase activation and superoxide production, and no longer protected the brain.

- In the long-term estrogen deprived animals, it was found that there was a significant loss in the hippocampus of one of the receptors for estrogen, thereby leading to the lost sensitivity to estrogen.

- In addition, another region of the hippocampus, the CA3 region, which is normally resistant to stroke damage, became hypersensitive to damage by stroke in the animals that had been deprived of estrogen for an extended period.

Thus, the study demonstrated that a long period of estrogen deprivation led to a loss of estrogen's sensitivity and protective effects in the hippocampus, and that some parts of the hippocampus that are normally resistant to stroke damage, lose this resistance when deprived of estrogen for a prolonged period of time.

Conclusions

According to Dr. Brann, "Every study has potential limitations, including ours. Our studies were performed in animals and it is unclear if the results are applicable to humans. Further research is needed to address this issue." Nevertheless, said Brann, "The study provides support for the idea that there is a "critical period" for beneficial effect of estrogen upon the brain and provides insights to the mechanisms underlying this critical period." He added, "It suggests studies in humans should focus on replacing estrogen prior to or at the time of menopause to examine for potential beneficial effects upon the brain."

Source: American Physiological Society (news : web)

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