Long periods of estrogen deprivation jeopardizes brain receptors, stroke protection

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Prolonged estrogen deprivation in aging rats dramatically reduces the number of brain receptors for the hormone as well as its ability to prevent strokes, researchers report.

However the damage is forestalled if estrogen replacement begins shortly after hormone levels drop, according to a study published in the journal *Proceedings of the National Academy of Sciences*.

"This is further evidence of a critical window for estrogen therapy, either right before or right after menopause," said Dr. Darrell W. Brann, Chief of GHSU's Developmental Neurobiology Program and the study's corresponding author.

The surprising results of the much-publicized Women's Health Initiative - a 12-year study of 161,808 women ages 50-79 - found hormone therapy generally increased rather than decreased stroke risk as well as other health problems. Critics said one problem with the study was that many of the women, like Brann's aged rats, had gone years without hormone replacement, bolstering the case that timing is everything.

Brann's earlier work in the hippocampus, a center for cognition, learning and memory, also showed a reduction in hormone receptors in younger rodents that were models of surgical menopause but left questions about why the loss occurred and whether it occurred naturally with aging. The new study documents that loss as unused receptors become targets for elimination in rats mimicking 60-65 year olds, about a decade past menopause. Interestingly, the receptor loss did not occur in the uterus, which remained sensitive to estrogen.

After long periods without estrogen, researchers found that an enzyme called CHIP - carboxyl terminus of Hsc70 interacting protein - increased binding with estrogen receptor alpha, a major brain receptor for neuroprotection. While CHIP levels remain unchanged, the increased binding results in about half the receptors getting hauled to the cell's proteosome to be chopped up and degraded. "We think this is the mechanism for how the receptor gets degraded," Brann said.

When researchers later treated the aged rats with estrogen, they found what the Women's Health Initiative showed: increased mortality. "So it did not seem to do anything good and maybe it did some harm in older rats and that is similar to what the WHI found," Brann said. The brain protection afforded by estrogen when given earlier to the rats, suggested the "critical window." Additionally when CHIP activity was blocked, so was the receptor destruction.

Next steps include estrogen-treating those rats where CHIP-related destruction is blocked to see if salvaged receptors will respond and looking at the process in other areas of the brain.

"We think the estrogen receptor decrease is why the sensitivity decreases," said Brann, who also is Associate Director of GHSU's Institute of Molecular Medicine and Genetics. "If the hormone is gone long enough it is logical there would be decreased sensitivity as normal feedback between the receptor and hormone is reduced."

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