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HRT prevents decline in memory of older women with "normal" memory

Toronto, ON (March 26, 2009) - A new study suggests that older women with memory abilities that would be considered normal for their age may benefit from the protective effects of estrogen.

"The findings suggest that the estrogen exposure through hormone replacement therapy (HRT) benefited older women with normal memory functioning by reducing the normal age-related decline that they would have experienced over a two-year period. However, these beneficial findings were limited to women with healthy brain cells, without any sign of decline in memory recall," says Dr. Mary Tierney, principal investigator of the study and director of the Geriatric Research Unit at Sunnybrook Health Sciences Centre.

The researchers examined whether a dose of HRT that would produce hormone levels equivalent to those in premenopausal women administered over a two-year duration would produce beneficial effects in older women with normal to mildly impaired memory. Women treated with HRT who at the beginning of the trial had normal to above average verbal memory test performance showed significantly higher scores after both the one-year and two-year points than a placebo group, whereas HRT had no significant effect on the performance of women who scored below average at the initial screening test.

Depletion of estrogen is considered an important contributing factor to the increased incidence of Alzheimer's disease (AD) in postmenopausal women. Failure to show treatment benefits of estrogen in several trials of women with or at risk of AD has led several researchers to hypothesize that the brain may lose its responsiveness to estrogens over prolonged periods of hormone deprivation.

"Estrogen has been shown to exert a protective effect on healthy brain structures", explains Dr. Tierney, who is also a Professor in the Department of Family and Community Medicine at University of Toronto. "Once cognitive impairment becomes clinically apparent, it seems that the targets for estrogen action might no longer be present, which would explain why estrogen treatment may not be effective in patients with cognitive impairment or AD."

To be published in an upcoming print edition of *Psychoneuroendocrinology*, the study is currently available online. The study was funded by the Canadian Institutes of Health Research. The double-blind trial of 142 women aged 61 to 87 involved randomly assigning participants to receive either a hormone therapy (estrogen and progesterone) or daily placebo for two years. Women were excluded if they met criteria for dementia, had a clinical history of any medical condition that might affect their cognition, or had a medical condition that was considered unsafe for them to take estrogen.

One hundred and thirty three of the women completed one year of the trial; 128 of the women completed two years. The primary measurement of outcome involved testing delayed verbal recall because it is considered to be one of the best indicators of the brain structure most associated with the beneficial effects of HRT. The effects of age, education and prior HRT use were all factored in when conducting the data analyses in this study.

The findings of this trial are different from those of the Women's Health Initiative (WHI) study conducted several years ago, which reported that HRT did not produce beneficial effects in older women and may have resulted in greater deterioration in those who developed vascular dementia. Dr. Tierney explained that the formulation of HRT was different in this study than that used in the WHI study. The WHI used a form of progesterone in their HRT that is known to antagonize the beneficial effects of estrogen on the brain. The study conducted at Sunnybrook used a form of estrogen that was molecularly similar to the estrogen found in premenopausal women and a form of progesterone that has been shown to be neuroprotective.

"The use of cyclical administration of the drugs might also be important factors in contributing to the beneficial outcomes seen in this trial," says Dr. Tierney. The investigators used cyclical as opposed to continuous hormone administration as research has shown that sustained hormone exposure down-regulates the corresponding brain systems, potentially reducing the efficacy of the hormones, and therefore they wanted to minimize this.

While it has been suggested that the critical period for the beneficial effects of estrogen exposure may be soon after the menopausal transition, the findings of this study suggest that this period may extend beyond the menopausal transition for women with normal memory functioning.
The women who benefited from HRT were on average 71 years of age and over 20 years post menopause. Why some women experience greater cognitive decline after menopause than others is not known but evidence suggests that many factors may be involved including diet, physical activity, social interaction, as well as postmenopausal variability in estrogen levels.

There were no significant differences in serious adverse events between the treated group and those given placebo. Symptoms usually associated with HRT were seen as expected. The limitations of this study were that it was a single-centre study and the participants were well educated and almost exclusively white. The results suggest that further studies of at least one-year duration focus on the effects of HRT in healthy older women who score at or above average on verbal memory tests. Further study is needed before recommendations can be made in a clinical setting.

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