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Oestrogen therapy affects brain structure but not function

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Abstract

According to new research, oestrogen therapy in postmenopausal women is associated with ventricular enlargement and increased white matter hyperintensities in the brain, but not with cognitive decline. This disconnect between structural and functional effects suggests that brain-derived lipids can be harnessed to meet the bioenergetic demand imposed by normal cognition.

The use of oestrogen hormone replacement therapy to treat menopausal symptoms is controversial: some studies have linked hormone replacement therapy with cognitive benefit, whereas others have linked it with cognitive decline. A new ancillary study to the Kronos Early Estrogen Prevention Study (KEEPS), conducted by Kantarci and colleagues at the Mayo Clinic Rochester, USA[1], contributes to a growing body of evidence regarding the complexity of neurological outcomes induced by hormone therapy interventions in postmenopausal women.

The KEEPS ancillary MRI study (KEEPS-MRI) included 95 women aged 42–59 years who were 5–36 months past menopause[1]. The participants were randomly assigned to conjugated equine oestrogens (CEE; $n = 29$), 17β-oestradiol therapy ($n = 30$) or placebo ($n = 36$). The hormone therapy was associated with increased ventricular expansion, brain volume decline and white matter hyperintensity (WMH) volume. Remarkably, despite reductions in brain volume in the women on oestrogen therapy, no differences in cognitive function were detected between the groups.

At baseline, global cognition and whole brain volumes did not differ between the placebo and oestrogen therapy groups[1]. However, ventricular volumes were larger in the 17β-oestradiol group than in the CEE and placebo groups, and women allocated to the CEE group had larger WMH volumes before initiation of treatment than did the other two groups. These baseline differences suggest that oestrogen therapy could be exacerbating a pre-existing condition.

The KEEPS-MRI data are consistent with the Women's Health Initiative Memory Study (WHIMS) ancillary MRI study (WHIMS-MRI), which detected reduced frontal lobe and hippocampal volumes and overall brain volumes in women aged 71–89 years who were on

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Competing interests statement

The author declares no competing interests.

hormone therapy[2]. Interestingly, in WHIMS-MRI, the reductions in brain volume associated with hormone therapy were greatest in women with the lowest baseline cognitive function, again suggesting that oestrogen therapy was aggravating a pre-existing vulnerability.

Other studies, including the small Duke University study and the much larger Cardiovascular Health Study (CHS), have reported declines in brain volume in association with oestrogen therapy[3,4], although this finding is by no means universal[5,6]. In the CHS cohort[4], 67 of current oestrogen users and 42 of past oestrogen users had previously undergone a hysterectomy[4]. This unusual demographic could be relevant to findings that hysterectomy before perimenopause — but not after menopause — is associated with an elevated risk of Alzheimer disease (AD) and, by extension, AD-related pathologies[7].

The disconnect between the structural and cognitive effects of oestrogen therapy in KEEPS-MRI is reminiscent of earlier studies that observed the same phenomenon. In both the Duke University study[3] and the CHS[4], cognitive function remained within the normal range in women receiving oestrogen therapy. In fact, in the CHS, current users of oestrogen therapy had higher Mini-Mental State Examination scores than did nonusers, and past oestrogen users had higher scores than either current users or never users[4].

The new report and its predecessors raise the following question: how can the brain sustain normal cognition while simultaneously undergoing AD-like processes, such as ventricular expansion, decline in brain volume, and increase in volume of WMHs? Mechanistic analyses at the basic science level might provide a plausible explanation. Before the perimenopause, oestrogen promotes glucose metabolism and mitochondrial function while suppressing ketone body metabolism in the brain. During the perimenopausal transition, oestrogenic promotion of glucose metabolism and suppression of ketone body metabolism in the brain are lost. At the menopause, the lack of oestrogenic suppression causes the ketone metabolic system to be reinstated and mitochondrial function to be restored[8]. The now-activated ketone metabolic system allows the brain to utilize ketone bodies as an alternative fuel[8,9].

Ketone bodies are derived from fatty acids contained within lipids. Typically, ketone bodies are supplied to the brain through metabolism of peripheral lipids by the liver. However, the lifting of suppression of ketone metabolism in the female brain at menopause allows the brain to utilize its own source, of lipids — namely, white matter — to generate ketone bodies to fuel the energetic demands of synaptic transmission, thereby enabling the brain to sustain generation of the necessary ATP for cognitive function[8,9]. The lack of difference in cognitive function between placebo and oestrogen users might be explained by the ability of the female brain to catabolize its white matter for fuel[8,9]. It is possible that oestrogen is potentiating the function of mitochondria in glial cells, as these mitochondria are capable of lipid-derived fatty acid metabolism and β-oxidation in the brain, thereby exacerbating development of WMHs.

This model does not, however, explain why the structural brain changes were more pronounced in in oestrogen users than in the placebo group in KEEPS-MRI[1]. At 48 months, the placebo-treated women did exhibit some decline in whole brain volume and expansion

of ventricular volume, and oestrogen seems to accelerate changes in brain structure that are already occurring in the ageing female brain.

> **“** We have yet to fully address the question of which women … benefit from … hormone therapies ”

We have yet to fully address the question of which women are most likely to benefit from oestrogen or other hormone therapies. In an analysis of a cohort of healthy post-menopausal women in the ELITE trial, three distinct clusters of women were identified on the basis of clinical indicators of metabolism[10]. A large cluster of women was metabolically healthy, a second cluster was at risk of cardiovascular disease, and a third was at risk of metabolic syndrome[10]. Deficits in cognitive function were only apparent in the cluster of women at risk of metabolic syndrome, and the decline in cognitive function within that cluster was largely driven by women who carried the apolipoprotein E ε4 allele (*APOE* 4*)[10], which is a well-established risk factor for AD and makes a particularly large contribution to AD risk in women. In the *APOE* 4*-carrying women, the dual challenge of dysfunction in both the metabolic and cholesterol transport systems proves to be a tipping point, as manifested in deficits in cognition, which is the most energetically demanding function of the brain. However, the effects of oestrogen or other hormone therapy on cognition in *APOE* 4*-carrying women remain to be determined.

This early-stage study provides proof of concept for a precision medicine approach to identify women for whom oestrogen or other hormone therapy is appropriate, and to define the right dose, regimen, formulation and timing of treatment. The time has come to bring the power of this approach to the issue of hormone therapy to address concerns that are critical to women’s neurological health.

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