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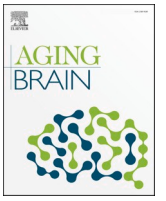

Why women may be more prone to Alzheimer's disease

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Women have a 2–3-fold greater propensity to develop Alzheimer's disease (AD), as compared to men [1,2]. Menopause, accompanied by marked reduction in the production of estrogen, is a risk factor for AD. While estrogen is essential for the healthy functioning of neurons [3], the mechanisms underlying sex differences in AD pathogenesis remain elusive.

Recently, in the journal *Science Advances*, Lattore-Leal et al. [4] demonstrated that overexpression of the cholesterol-metabolizing enzyme CYP46A1 protects aged female mice from developing Alzheimer's-like disease [4]. The transgenic animals displayed higher levels of estrogen, healthier neurons and improved memory. These observations are consistent with previous studies reporting that AD is associated with dysregulation of brain cholesterol turnover and reduced CYP46A1 levels [5,6]. In contrast to the females, *CYP46A1* transgenic males showed increased anxiety-like behavior and a worsening of hippocampus-dependent memory [4].

At the biochemical level, CYP46A1 in the brain metabolizes cholesterol to 24S-hydroxycholesterol (24S OH-Chol) [7,8]. The latter is a signaling molecule that binds to the transcription factors liver X receptor (LXR) and retinoic acid–related orphan receptor (RORα and RORγ), as well as to N-methyl-d-aspartate receptors (NMDAR). Activation of these receptors reportedly alters brain metabolism and synaptic function [9–11]. For example, LXR activation promotes the synthesis of neuroactive steroids [12], including that of estrogen and testosterone, both of which exert neurotrophic effects [13–15].

Interestingly, the authors observed sexually differential expression of the enzymes responsible for the generation of dihydrotestosterone (DHT, a "pure" androgen) from testosterone in the hippocampus of male and female *CYP46A1* transgenic mice: *CYP46A1* overexpression was found to decrease 5α-Reductase (Srd5a1, converting testosterone to DHT) and hydroxy-steroid dehydrogenase-17β-10 (Hsd17b10, which converts 3α-androstanediol to DHT) in females; on the other hand, *CYP46A1* overexpression in males increased Srd5a1 and Hsd17b10 expression (presumably stimulating DHT synthesis (see Fig. 3 in ref. [4]). These observations provide a likely explanation for sex differences in the outcome of *CYP46A1* upregulation. Further, in primary neuronal cultures, Lattore-Leal et al. [4] found that DHT opposes the upregulation of estrogen receptor expression, effectively countering estrogen-mediated neuroprotection (see Fig. 4 in Ref. [4]). Adding a translational element to their work, Lattore-Leal et al. [4] observed higher levels of 24S OH-Chol in the cerebrospinal fluid (CSF) of a sub-group of female AD patients. These subjects were characterized by lower CSF levels of phosphorylated tau, a biomarker that increases with severity of AD pathology.

Overall, the results of this new work [4] aligns with earlier studies that showed the beneficial effects of CYP46A1 on memory performance during aging and reduction of AD-like features in female mice [16,17]. Intriguingly, however, pharmacological activation of CYP46A1 with low doses of efavirenz, an anti-retroviral drug, suggests that upregulated CYP46A1 activity may provide equal benefit to female and male mice [18]. However, the results of the latter study must be cautiously interpreted since it only involved small numbers of animals and not all reported parameters were obtained in both sexes. Meanwhile, the work of Lattore-Leal and colleagues [4] warrants deeper exploration of the preventative and/or therapeutic potential of modulated activity of CYP46A against AD; since women are 2–3 times more vulnerable to developing AD, such a strategy could help make an impact on reducing the occurrence of AD at the population level.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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