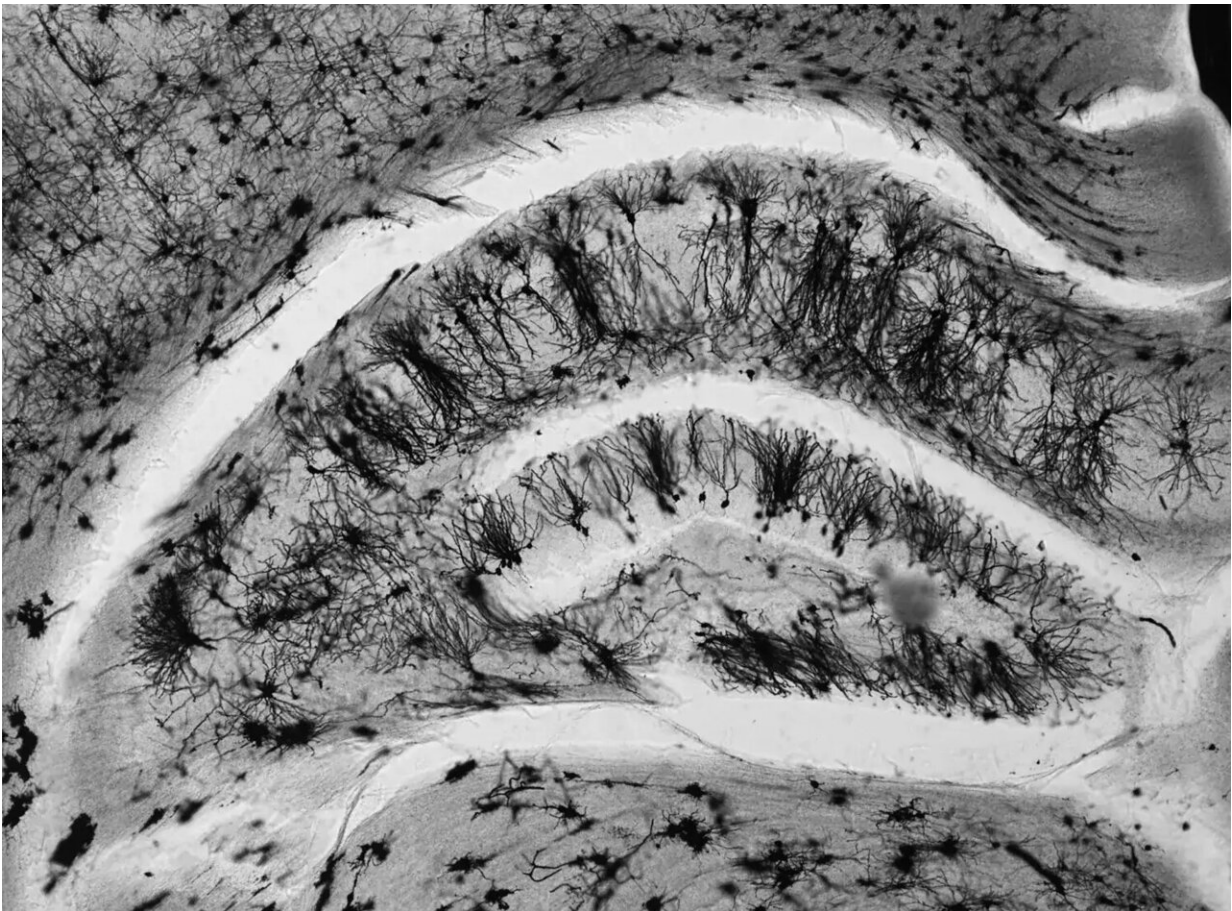


Protein activation in the brain may protect women against Alzheimer's

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Golgi staining of mouse brain tissue. Credit: Silvia Maioli laboratory

A new study at the Karolinska Institute suggests that activation of a certain brain protein can protect women from developing

neurodegenerative diseases such as Alzheimer's disease.

"Cholesterol turnover and sex hormones are modifiable factors. Our results suggest that they may serve as potential treatment targets for several neurodegenerative diseases in the future," says Silvia Maioli, Associate Professor at the Department of Neurobiology, Care Sciences and Society at Karolinska Institutet and principal investigator for the study.

The study, which is based on [mice](#), shows that activation of the [brain protein](#) CYP46A1 can protect women from developing [neurodegenerative diseases](#) such as Alzheimer's disease. The research is [published](#) in the journal *Science Advances*.

The protein converts brain excess cholesterol into a cholesterol product called 24S-hydroxycholesterol (24OH). The study was conducted in male and female mice by increasing the levels of the protein CYP46A1 which in turn increases the production of 24OH. In the females, the researchers were able to observe healthier neurons, improved memory capacities and higher estrogen activity, both in menopause-like conditions and during aging. These effects were not seen in male mice.

Measurements of 24OH in the [cerebrospinal fluid](#) of patients with Alzheimer's disease showed that higher 24OH levels correlated with lower levels of Alzheimer's markers such as tau, but only in women.

Two-thirds of individuals with Alzheimer's disease are women, and early menopause is a specific risk factor for cognitive decline. Menopause is characterized by the loss of estrogen, a hormone produced not only in the ovaries but also in the brain, which is essential for maintaining healthy and functional neurons .

The study shows that the activation of CYP46A1 increases estrogen

activity in the brain of menopausal and elderly [female mice](#), making CYP46A1 a potential female-specific therapeutic target.

"Previous research has shown that CYP46A1 can be activated pharmacologically with low doses of the anti-HIV drug Efavirenz," says Silvia Maioli. "We believe that targeting cholesterol metabolism by CYP46A1 activators such as Efavirenz may offer a new approach to promote estrogen-mediated neuroprotection in women at risk of Alzheimer's disease."

More information: María Latorre-Leal et al, CYP46A1-mediated cholesterol turnover induces sex-specific changes in cognition and counteracts memory loss in ovariectomized mice, *Science Advances* (2024). [DOI: 10.1126/sciadv.adj1354](https://doi.org/10.1126/sciadv.adj1354)

Provided by Karolinska Institutet

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