

HORMONES

Estrogen modulates cognitive function in mid-age female mice

Itoh, N. et al. *Nat. Commun.* **14**, 6044 (2023)

Brain aging is a main concern nowadays because humans live longer lives, which translates to more age-associated cognitive decline. With more time for aging and neurodegeneration to have an impact, it is urgent to better understand what is causing neurodegeneration and how to revert it. Sex hormones are known to decline with age, leading to menopause and andropause, which are associated with many physiological changes and have been linked to cognitive decline. In women, estrogen is considered to be neuroprotective, and menopause is associated with cognitive deficits and brain atrophy. A study in *Nature Communications* now shows that the loss of ovarian hormones has an age-dependent effect, leading to hippocampal-dependent cognitive impairment and synaptic loss in mid-age but not in young female mice.

Using healthy and gonadectomized (GDX) C57BL/6J mice at three age stages (young, midlife, and old), researchers compared the effects of hormonal decline on cognition and neuronal structures using behavioral and imaging techniques. They showed that during aging there are sex differences in the atrophy of the dorsal hippocampus, known for its role in cognition and memory. Notably, males showed gradual atrophy from young to midlife to old ages. Additionally, gonadectomy showed an effect on cognition in only midlife females, performing similarly to old females in spatial and working memory tasks. Then, they showed that deletion of the estrogen receptor β (ER β) in hippocampal astrocytes reduced the neuroprotective effect of estrogen in midlife females and that *enolase 1* was differently expressed in astrocyte-ER β cKO compared to WT animals. Finally, they found that treating

GDX females with Er β -ligand reversed the hippocampal pathology, with females even performing similar to vehicle-treated sham females in a Morris water maze test.

With longer lifespans and better healthcare, finding therapies that fight cognitive decline and allow people to live a better life is important. With menopause being a mandatory transition in a woman's life, this work sheds light on the importance of sex hormones in cognition. It also adds to the existing knowledge regarding the timing of treatment, as women could benefit more from a treatment closer to menopause age instead of after menopause, where cognitive issues are already in place.

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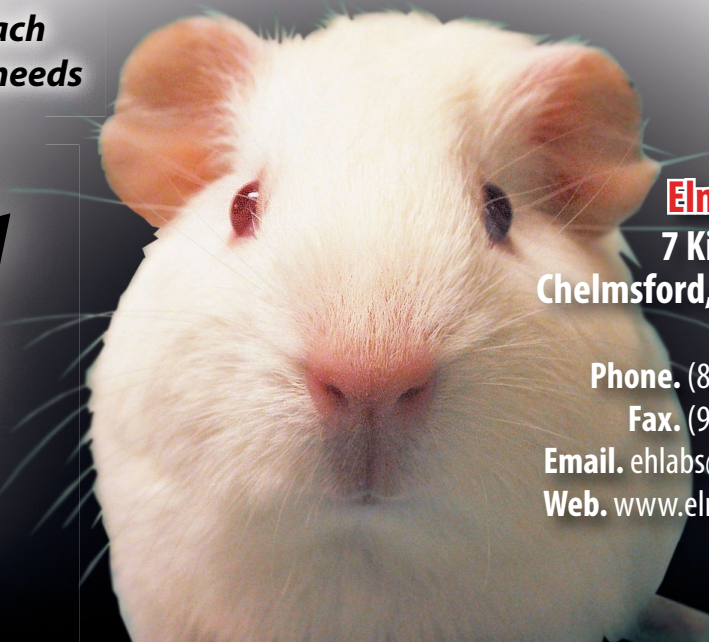
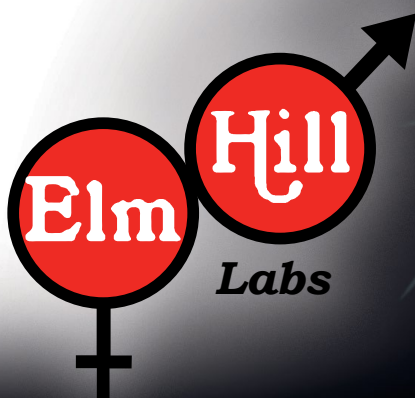
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