

## Neurobiology

# Why Women Are Predisposed to Alzheimer's Disease

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*Alzheimer's disease leads to progressive dementia, profound disability and impaired quality of life. Globally, there are more than 50 million cases, over two thirds of which are women. The cause behind this gender difference had remained unclear for decades, until we discovered that a specific hormone, which dramatically increases in women after menopause, triggers this phenomenon.*



Alzheimer's disease (AD) is a brain disorder that progressively damages memory and thinking capabilities, eventually leading to losing the ability to communicate and carry out the daily activities. The prevalence of AD is significantly higher in women compared to men; more than two thirds of the patients diagnosed with AD are women, yet the exact cause remains unknown. Men and women with AD exhibit different cognitive and psychiatric symptoms, with women showing faster cognitive decline after diagnosis. Due to the predisposition of women to AD, the sex hormone estrogen has become the primary focus of research, despite the lack of evidence linking estrogen to an increased risk of cognitive impairment and dementia in

women. FSH (known as the follicle stimulating hormone) is another sex hormone, which is secreted by a small gland located in the brain. It is a central regulator of male and female reproduction and its primary function is to induce estrogen production from the ovaries in females and regulate spermatogenesis in males. The FSH level in serum (that is, blood without blood cells and clotting agents) starts to rise about two to three years before menopause, when serum estrogen levels are still normal. During menopause, estrogen is dropping but FSH continues to remain high. This discrepancy in hormone levels made FSH to be regarded as a marker for the onset of menopause.

AD is caused by the abnormal accumulation of proteins within and around brain cells, a disease with no cure available up to now. One of the proteins involved, called amyloid, forms deposits growing into plaques around brain cells. Another protein, called Tau, forms tangle-like deposits within brain cells that slowly aggregate and destroy them. How these proteins are accumulated and whether they are the causes or results of this devastating disease remains unclear. To examine this phenomenon, we established the following theory: a chronic inflammation in the brain activates a transcription factor (a protein that helps to regulate genes by binding to nearby DNA) named C/EBP $\beta$ , and its downstream effector (an enzyme that accelerates the progression of AD), named C/EBP $\beta$ /AEP. The former increases the levels of precursors of the Tau and amyloid proteins, and the latter cuts the proteins to pieces that act as toxic aggregates.

Epidemiology studies reveal that women experiencing surgical menopause (that is, ovary removal surgery) at an earlier age show faster decline in global cognition and increased AD neuropathology. In estrogen-free women with AD, FSH levels are significantly higher. FSH can trigger osteoporosis via increasing bone resorption (a process that leads to decreased bone mass and density) and regulate body fat. Interestingly, an earlier study showed that blocking FSH action on its receptor via its specific antibody not only increases bone mass, but also reduces body fat. In light of this discovery, we wanted to explore whether FSH could activate the above indicated C/EBP $\beta$ /AEP signaling of our suggested theory. First, we tested FSH's effect in brain cells and found that FSH stimulated the provocative signaling, resulting in amyloid and truncated Tau escalation, resembling the phenomena observed

in AD patient brains. Consequently, we extended the experiments to mice with AD and found that FSH protein administration accelerated the disease onset and facilitated cognitive defects in both male and female mice. Next, we studied the relation between ovary removal and cognitive decline by conducting an ovariectomy surgery to female mice, followed by FSH antibody treatment that blocked the action of FSH. We found that ovary resection-triggered AD symptoms were strongly attenuated by the FSH antibody. Then, we depleted the FSH receptors (or else FSHR) from the mice and found that ovary resection-triggered AD was blunted in the mice lacking these receptors in the brain. This important finding underscored that FSH triggers AD onset via activating FSHR signaling. To further ascertain that this effect is indeed mediated by C/EBP $\beta$ /AEP signaling in the brain, we partially deleted C/EBP $\beta$  gene from mice with AD, to prevent the C/EBP $\beta$  protein activation. We found that neither FSH administration nor ovary removal could induce AD in these animals, indicating that C/EBP $\beta$ /AEP signaling is indispensable for FSH to trigger AD. Lastly, to alleviate the concern regarding estrogen implication in ovary section-elicited AD, we injected estrogen back into the mice and found that it failed to attenuate AD, suggesting that FSH elevation, and not estrogen deficiency, is accountable for triggering AD in mice.

Our recent findings, demonstrating that FSH surge drives AD in females and blockade of it via FSH antibody alleviates cognitive dysfunctions, provide a clear explanation why women are predisposed to Alzheimer's disease. Excitingly, this new discovery not only establishes a causal role for rising serum FSH levels in AD pathology, but also unmask opportunities for treating AD, obesity, hypercholesterolemia and osteoporosis with a single FSH blocking agent.