Perimenopausal Estradiol Loss Links the HPG Axis to Mitochondrial Failure and Amyloid Clearance in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) disproportionately affects women, with risk accelerating during the perimenopausal transition when estrogen levels decline. We hypothesize that reduced gonadal hormone signaling impairs hippocampal activity and downstream mitochondrial resilience, thereby promoting calcium dysregulation, oxidative stress, and amyloid accumulation. To test this idea, we extend a minimal hypothalamic–pituitary–gonadal (HPG) axis model, formulated as a system of ordinary differential equations, to include a hippocampal signal variable driven by estradiol. The core model describes hypothalamic releasing hormone, pituitary gonadotropins, gonadal hormones, and glandular mass dynamics with nonlinear feedback. The hippocampal extension is represented as a leaky integrator of estrogen, allowing reduced estrogen to diminish hippocampal output. This signal is then coupled to mitochondrial calcium and amyloid dynamics, where it exerts a protective effect by reducing calcium overload and enhancing amyloid clearance. Numerical simulations demonstrate that declining estradiol leads to progressive reductions in hippocampal activity, heightened calcium imbalance, and accelerated amyloid burden. Sensitivity analysis identifies a key parameter controlling the strength of hippocampal–mitochondrial coupling and suggest windows in which hormone replacement therapy may mitigate neurodegenerative progression. By linking endocrine decline to hippocampal dysfunction and impaired proteostasis, this model provides a mechanistic framework for understanding female-specific vulnerability in AD and offers a quantitative tool for testing intervention strategies.

Introduction

7.2 million Americans 65 years of age or older, or 11percent of Americans 65 years and older, are diagnosed with Alzheimer's in America. In 2022, Alzheimer's disease was categorized as the seventh-leading cause of

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death in the United States, with 120,122 deaths from the disease in that year alone.[1]

Alzheimer's is a memory loss disease caused by neural death and synaptic dysfunction.[2] Lysosomal deacidification contributes to an accumulation of misfolded proteins from amyloid plaques in the extracellular membrane and neurofibrillary tangles inside the nerve cells.[3] The accumulation of misfolded proteins causes inflammation in the brain. Consequently, the inflammation leads to apoptosis of the neurons. [3]

Genetics plays an important role in Alzheimer's disease.[4] Specifically, the APOE gene, which transports cholesterol to various parts of the body, has been identified to affect the risk for Alzheimer's, Lewy Bodies Dementia (LBD), and Parkinson's.[5] The APOE gene has three alleles: e2, e3, and e4. The e2 allele has the lowest risk for Alzheimer's, LBD, and Parkinson's. The e3 allele is the most common, with an average risk for the diseases. However, individuals with the e4 allele are at a higher risk for Alzheimer's, LBD, and Parkinson's.[5] Since the e4 gene showcases the effects in neurodegenerative symptoms later in life, after an organism has reproduced, it wasn't removed by evolution.

The accumulation of misfolded proteins classifies Alzheimer's as a prion disease. Alzheimer's disease can be traced back to mitochondrial dysfunction.[6] In the mitochondria, degradation of the Krebs cycle reduces the ATP energy available to break down the amyloid proteins. The mitochondria associated membranes (MAMs) is a bridge between the endoplasmic reticulum (ER) and mitochondria that transfers calcium ions from the ER to the mitochondria.[6] Calcium ions increase the rate of the Krebs cycle, but they also increase the number of reactive oxygen species (ROS), which damage the mitochondria.[7] Calcium influx begins a positive feedback loop. As one mitochondrion is damaged, the rest need more calcium ions to increase the energy produced. The subsequent influx of calcium ions causes more mitochondria to dysfunction. This calcium influx can be a result of various reasons. For example, individuals can possess the genetic variance that causes the MAM to be abnormally large or leaky. Insulin resistance can also play a role in calcium influx. Glucose spikes increases the amount of calcium needed, causing a larger number of calcium ions to travel into the mitochondria.[8] The dysfunction of the mitochondria causes lysosomal deacidification. When lysosomes are deacidified, they lose their ability to break down cellular waste, contributing to the build-up of misfolded proteins[3] (see Figure 1).

The Hypothalamic-Pituitary-Gonadal (HPG) axis regulates the production of the sex hormones, like estrogen. [9] The hypothalamus produced the Gonadotropin-Releasing Hormone (GnRH), commonly referred to as x_1. The x_1 hormone stimulated the pituitary gland to release two more hormones, the Luteinizing Hormone (LH) and the Follicle Stimulating Hormone (FSH). Both of these hormones are referred to as x_2. The x_2 hormones act on the gonads, the ovaries in females and testes in males, to release the sex hormones, referred to as x_3. The HPG axis utilizes a system known as double reinforcement. The presence of x_1 not only stimulates the pituitary gland to release x_2, it also makes the pituitary cells divide. The rising

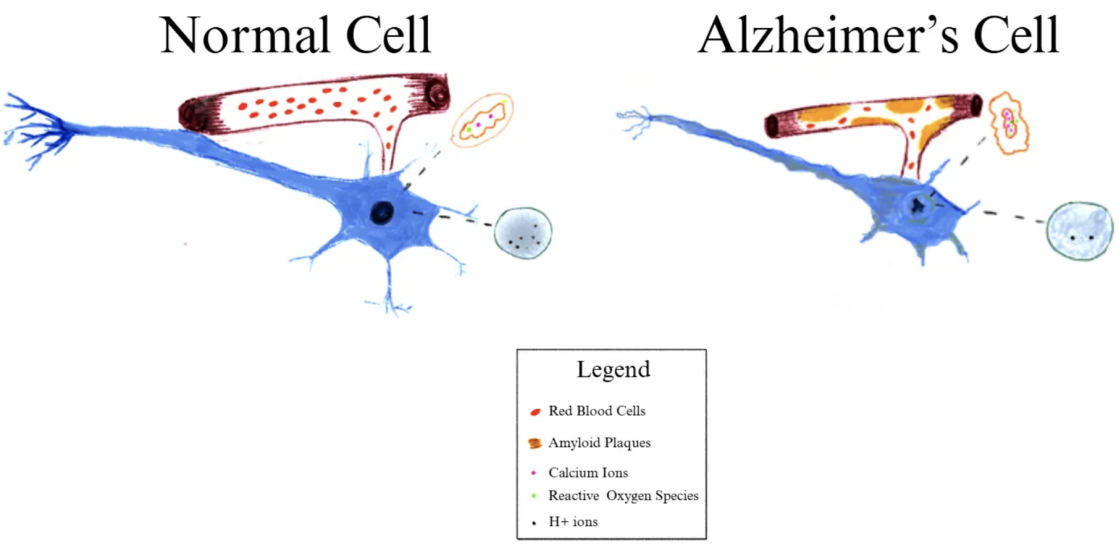

Figure 1: Schematic comparison of a healthy neuron and an Alzheimer's-affected neuron, highlighting increased amyloid plaques, altered calcium/ROS signaling, and impaired cellular homeostasis in the disease state.

number of cells causes an increase in the size of the pituitary gland and the number of x_2 cells produced. Similarly, the presence of x_2 cells stimulates the gonads and results in an increase in the size of the gonads by making the G cells divide. The HPG axis is an example of a negative feedback loop[9]. The release of testosterone or estrogen represses production of hormones by the hypothalamus and the pituitary gland.[9] The HPG axis results in the production of estrogen, which plays a large role in slowing the progression of neurodegeneration and supporting hippocampal health.[10] Estrogen supports the function of SIRT proteins in the mitochondria, which reduce mitochondrial ROS, as well as regulate the intake of calcium in the mitochondria.[11] In this paper, we will explore how low estrogen increases the chances of someone having Alzheimer's disease.

Methods

We developed a mechanistic dynamical model linking endocrine changes in the HPG axis to hippocampus and, in turn, to mitochondrial calcium homeostasis and amyloid burden (see Figure 2). The model is formulated as a system of ordinary differential equations (ODEs) and simulated numerically to compare a cycling (premenopausal) regime with a low-estrogen (post-menopausal) regime. All variables are treated as lumped, population-level signals (e.g., average hormone concentrations or effective tissue masses), and parameters represent effective gains, decay rates, and feedback strengths.

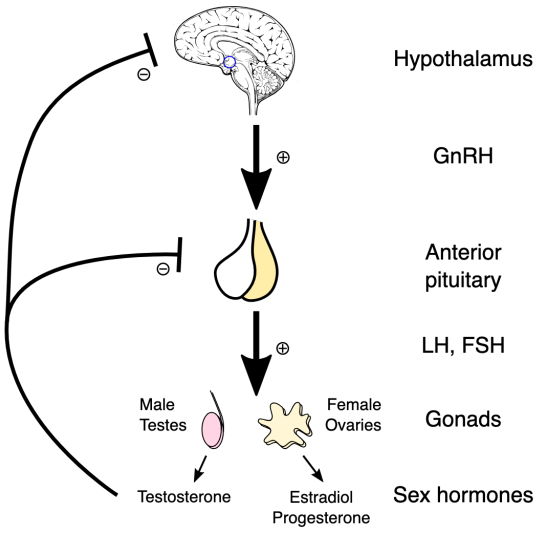

Figure 2: Hypothalamic–pituitary–gonadal (HPG) axis and its feedback control of gonadal hormones (estradiol/progesterone in females; testosterone in males), illustrating the pathway linking hormone production to brain function.

HPG axis model

We begin with a minimal hypothalamic–pituitary–gonadal (HPG) axis model [12] consisting of five coupled ODEs. The variables are: hypothalamic releasing hormone x_1 (GnRH), pituitary gonadotropins x_2 (LH/FSH), gonadal hormone x_3 (estradiol), pituitary functional mass P, and gonadal functional mass G. The dynamics are

$$\frac{dx_1}{dt} = q_1 \frac{H}{x_3} - \alpha_1 x_1, \tag{1}$$

$$\frac{dx_2}{dt} = q_2 \frac{P x_1}{x_3} - \alpha_2 x_2, \tag{2}$$

$$\frac{dx_3}{dt} = q_3 G x_2 - \alpha_3 x_3, \tag{3}$$

$$\frac{dP}{dt} = P(b_P x_1 - a_P), \tag{4}$$

$$\frac{dG}{dt} = G(b_G x_2 - a_G). \tag{5}$$

Here H is a constant hypothalamic drive. The parameters q_1, q_2, q_3 set production rates, and $\alpha_1, \alpha_2, \alpha_3$ are the clearance rates. The terms in (4)–(5) represent trophic "double reinforcement": hypothalamic and pituitary signals promote the growth of the corresponding endocrine glands, while a_P and a_G represent baseline turnover. Estradiol x_3 provides negative feedback by suppressing x_1 and x_2 through the divisive factor $1/x_3$ in (1)–(2).

Post-menopausal transition via loss of ovarian reserve

To model the transition to menopause, we generalize ovarian responsiveness by introducing an ovarian reserve factor $\phi(t) \in [0, 1]$ that scales the ability of gonadotropins to maintain ovariian mass:

$$\frac{dG}{dt} = G\big(b_G x_2 \phi(t) - a_G\big). \tag{6}$$

We represent declining reserve using a smooth sigmoid,

$$\phi(t) = \frac{1}{1 + \exp\big(k(t - t_m)\big)}, \tag{7}$$

where t_m denotes the midpoint of the menopausal transition and k controls how abrupt the decline is. In the cycling regime, $\phi(t) \approx 1$ and the model can support oscillatory hormone dynamics. In the post-menopausal regime, $\phi(t) \to 0$, ovarian mass G declines, and estradiol x_3 approaches a chronically low equilibrium.

Mitochondrial calcium and amyloid dynamics

To connect endocrine decline to downstream pathology, we add two additional state variables: mitochondrial calcium load $C(t)$ and amyloid burden $A(t)$. The model assumes that hippocampal support is protective by reducing calcium overload and enhancing amyloid clearance:

$$\frac{dC}{dt} = c_0 - c_1 h - c_2 C, \tag{8}$$

$$\frac{dA}{dt} = p_0 + p_1 C - p_2 h A. \tag{9}$$

In (8), c_0 is a baseline calcium influx/drive, c_1 quantifies the protective effect of hippocampal signaling, and c_2 is a clearance or relaxation rate. In (9), p_0 represents baseline amyloid production, p_1 couples elevated calcium to increased amyloid accumulation, and p_2 captures hippocampal-dependent amyloid clearance (modeled as a removal term proportional to both h and A). This structure ensures that sustained reductions in h can yield progressive increases in both C and A.

Results

We first simulated the model in a premenopausal (cycling) regime by keeping gonadal reserve constant ($\phi(t) = 1$). In this setting, the HPG axis settles into sustained oscillations (Fig. 3). Estradiol (x_3) exhibits large-amplitude, repeating peaks, while the upstream hypothalamic and pituitary hormones (x_1 and x_2)

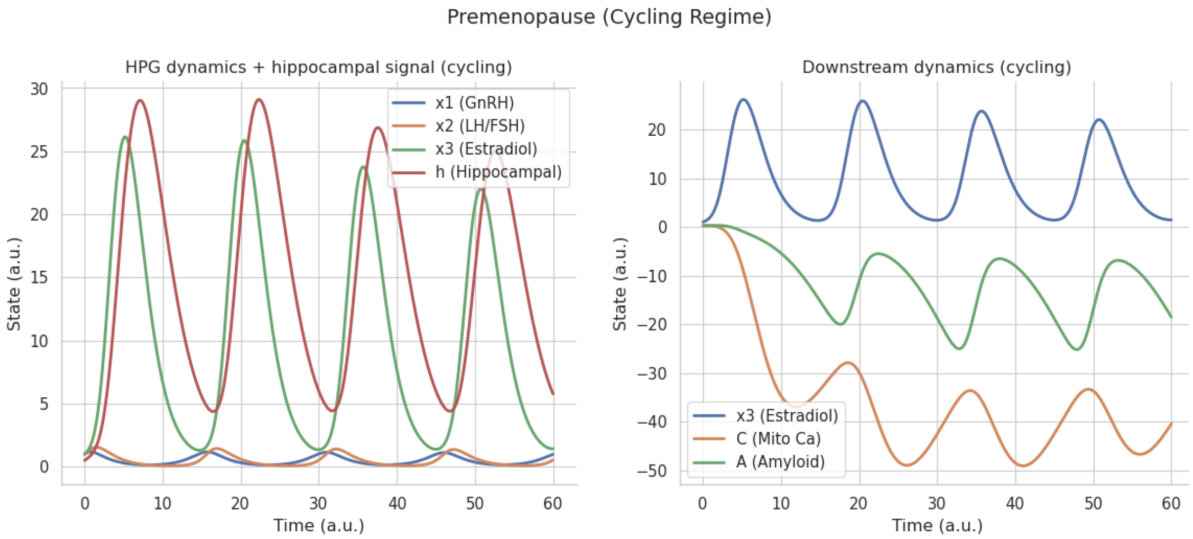

Figure 3: Premenopause (cycling regime). Left: HPG dynamics and hippocampal signal show stable oscillations; estradiol (x_3) drives the hippocampal support variable (h) as a smoothed, lagged response. Right: downstream variables (mitochondrial calcium load C and amyloid burden A) fluctuate but remain bounded over time in the cycling regime. All quantities are shown in arbitrary units from the nondimensionalized simulation.

oscillate with smaller amplitudes. Because the hippocampal variable h is modeled as a leaky integrator of estradiol, it tracks x_3 with a smoother waveform and a lag, producing rhythmic hippocampal support over the cycle (Fig. 3, left).

Downstream of the hippocampal signal, mitochondrial calcium load (C) and amyloid burden (A) also vary over time (Fig. 3, right). In the cycling regime, these downstream variables remain bounded and fluctuate periodically rather than drifting monotonically, consistent with the idea that recurring epochs of high estradiol produce recurring protective hippocampal input that prevents chronic calcium overload and sustained amyloid accumulation.

Postmenopause: reserve decline collapses estradiol and increases pathology readouts

Next, we simulated a postmenopausal transition by introducing a declining gonadal reserve factor $\phi(t)$ (Eq. (7)), which reduces the ability of gonadotropins to maintain gonadal mass. As reserve falls, gonadal mass G decreases, and estradiol x_3 collapses from cyclic peaks to a chronically low level (Fig. 4, left). Because h depends on x_3, hippocampal support also declines and approaches a lower steady state.

This endocrine collapse propagates into downstream pathology readouts (Fig. 4, right). As hippocampal support weakens, the model predicts a sustained shift toward higher mitochondrial calcium load and a progressive increase in amyloid burden (i.e., reduced clearance and greater net accumulation). In this regime, the downstream variables exhibit a transient phase during the transition and then approach a new, higher-

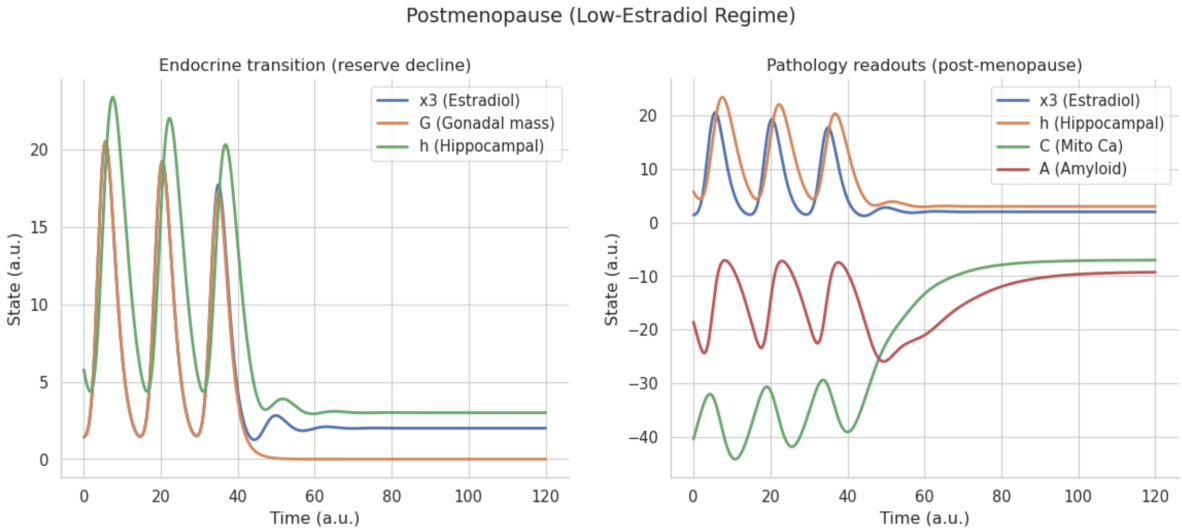

Figure 4: Postmenopause (low-estradiol regime). Left: declining reserve reduces ovarian mass G, leading to loss of estradiol oscillations and a chronically low estradiol level; hippocampal support h declines accordingly. Right: reduced hippocampal support is accompanied by a sustained shift toward higher mitochondrial calcium load C and increased amyloid burden A. All quantities are shown in arbitrary units from the nondimensionalized simulation.

burden steady state, rather than remaining purely oscillatory as in premenopause.

Simulation parameters and initial conditions

Table 1 lists the parameter values used to generate Fig. 3 and Fig. 4. Premenopause simulations used constant reserve $\phi(t) = 1$. Postmenopause simulations used a sigmoid reserve decline with midpoint t_m and steepness k. The premenopause simulation was run on $t \in [0, 60]$ and the postmenopause simulation on $t \in [0, 120]$ (arbitrary time units). Initial conditions for the premenopause run were

$$[x_1, x_2, x_3, P, G, h, C, A]_{t=0} = [1,\ 1,\ 1,\ 1,\ 1,\ 0.5,\ 0.3,\ 0.2].$$

The postmenopause simulation was initialized from the final state of the premenopause run to represent a transition from a cycling baseline.

Conclusion

We presented a simple mechanistic model that links female endocrine aging to downstream processes associated with Alzheimer's disease. Starting from a minimal hypothalamic–pituitary–gonadal (HPG) axis described by coupled ODEs, we introduced an estrogen-driven hippocampal support signal and connected this signal to mitochondrial calcium regulation and amyloid dynamics. In the premenopausal regime, the

Table 1: Parameter values used in the numerical simulations (arbitrary units).

Parameter	Meaning	Value
q_1, q_2, q_3	Production gains for x_1, x_2, x_3	1.0, 1.0, 1.0
$\alpha_1, \alpha_2, \alpha_3$	Clearance rates for x_1, x_2, x_3	0.5, 0.5, 0.5
H	Constant hypothalamic drive	1.0
b_P, a_P	Pituitary growth and turnover	1.0, 0.5
b_G, a_G	Gonadal growth and turnover	1.0, 0.5
c_0, c_1, c_2	Calcium drive, protection by h, clearance (Eq. (8))	0.20, 0.30, 0.10
p_0, p_1, p_2	Amyloid baseline, Ca-driven, h-dependent clearance (Eq. (9))	0.02, 0.20, 0.05
t_m	Menopause midpoint in $\phi(t)$ (Eq. (7))	40.0
k	Menopause steepness in $\phi(t)$ (Eq. (7))	0.6

model produces sustained hormone oscillations, yielding rhythmic hippocampal support that keeps calcium load and amyloid burden bounded. In contrast, when ovarian reserve is allowed to decline, the system transitions to a postmenopausal regime characterized by chronically low estradiol, reduced hippocampal support, and sustained increases in calcium dysregulation and amyloid accumulation.

The main contribution of this work is a quantitative framework that makes the causal chain from endocrine decline to neuronal vulnerability explicit and testable. The model predicts that the strength of hippocampal–mitochondrial coupling strongly shapes whether endocrine changes remain compensated or progress toward a higher-burden pathological steady state. This provides a principled way to explore intervention strategies, including hormone replacement therapy (HRT)[13], by representing treatment as an external estrogen input and evaluating its effect on downstream calcium and amyloid trajectories.

This study has several limitations. The model is intentionally low-dimensional and phenomenological: it aggregates many biological pathways into a small number of effective variables and does not explicitly represent key processes such as tau pathology, neuroinflammation, synaptic loss, or spatial heterogeneity across brain regions. Additionally, the parameters were chosen to demonstrate qualitative regimes rather than to fit a specific dataset. Future work should calibrate the model against longitudinal endocrine and biomarker data, extend the pathology module to include tau and inflammatory feedback loops, and incorporate stochasticity and individual variability to assess risk trajectories across populations. Despite these limitations, the proposed framework offers a transparent starting point for integrating perimenopausal endocrine dynamics with neuronal resilience mechanisms and for generating quantitative, falsifiable hypotheses about female-specific vulnerability in Alzheimer's disease.

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