Chapter 6

Neuroprotection in Perimenopausal Women

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Additional information is available at the end of the chapter

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Abstract

Endocrine and neural senescence overlap in time, by intertwined complex feedback loops. Womens' brain is genetically more prone to suffer during life, and perimenopause is a "critical period" in neuroaging, when the degenerative processes begin. Many hypotheses on the multifactorial nature of women's brain aging are elaborated, and tested in high-tech research centers. The most analyzed Alzheimer's disease (AD) is characterized not only by Aβ oligomers and fibrils accumulation, but also by metabolic and inflammatory changes, with the onset during menopausal transition and early years of menopause. Deep analysis of endocrine, neural, and metabolic pathways are giving new insights to the sequential view of Aβ-centric in AD pathogenesis, prevention, and treatment from perimenopause, for maintaining women's neurological health.

Keywords: neuroaging, perimenopause, critical period

1. Introduction: sex differences in contemporary neurodegenerative disorders

Ovarian aging is very well-known in contemporary women's life, and the jeopardizing menopausal effects of sex steroid hormones deficiency are clinically evident in late-life mental disorders. Endocrine and neural senescence overlap in time, and are mechanistically intertwined in complex feedback loops.

In the past century, both life expectancy and the average age of onset of menopause for women in many countries from Western Europe and North America were slightly over 50 years, whereas currently, women can expect to live until the age of 80 years, although the average age of menopause remains in the early 50s. Given the importance of the brain as a target organ

for sex steroids, it is not surprising that many of the complaints that prompt women to seek treatment related to menopause are neurological in origin.

Dementia with its most severe entities, such as the Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS), are the most frequent contemporary neurodegenerative disorders, connected in majority by neural cell loss and neuroinflammation.

There are sex/gender differences in cognitive trajectories in clinically normal older adults [1], and women are known to have a higher propensity to develop AD versus men [2, 3], a higher risk of mild cognitive impairment and a lower risk, but poorer outcomes after stroke [4]. Women's risk for AD is considered to be through their organizational effects during developmental sexual differentiation of the fetal brain [5].

The AD is the most prevalent form of old-life mental failure in worldwide humans, being a progressive neurodegenerative disorder, for which a number of genetic, environmental, and lifestyle risk factors have been identified. The estimated prevalence of all-cause of dementia varies from 4.7% in Central Europe to 8.7% in North Africa/Middle East, with North America falling at 6.4%. Currently, over 46 million individuals live with dementia worldwide and the number is projected to increase to 131.5 million by 2050 [6]. The AD is familial with early-onset and sporadic with late-onset, and the present chapter will discuss the sporadic AD with late-onset in women, the most common form of AD representing more than 95% of the current human AD population [7].

In this very moment, the geroscience research is imperative with aims to forward a better and full understanding of neurodegeneration/neuroprotection of "the sexome" [8], and to prevent or delay by every tool the deleterious effects of brain aging [9]. Estrogen deficiency or estrogen disrupters are associated from menopause transition with episodic memory troubles, a cognitive domain in which impairments are associated with the increased risk of AD, being less known the onset of the other neurodegenerative disorders [10].

AD has an insidious onset and a gradual progression over several years—from 1.5 to 8 or up to 10 years, or a preclinical stage with a subtle loss of cognitive functioning—as verbal memory on new information, that precede several years the AD diagnostic, period considered as a transition period from normal aging brain to AD [11]. During this period, there are discovered several subtypes of mild cognitive impairment (MCI), 10–15% with the risk to future evolution to AD per year [12], or a 12% conversion rate from MIC to dementia yearly [13]. The characteristic deposits of β-amyloid and tau proteins depicted by neuroimaging or at autopsy located in the hippocampus, medial temporal regions, parietal, and frontal cortical regions [14] may be prevented from extension, as other structural degenerative diseases. It is imperious to prevent the intracellular appearance of the amyloid peptide, which induces by its toxicity neuronal apoptosis and cell death, events that can be prevented by sex steroid hormones [15].

The clinical symptoms/signs of MCI are considered by neuroscientists as prodrome to AD [16], and their algorithms for diagnosis may permit to initiate the hormone/estrogen therapy (HT/ET), because their onset moment is coincidental to perimenopause, as considering the North American clinicians [17]. The "timing" theory regarding the reproductive stage and

role of time since menopause at initiation of HT/ET may work in preventing the mental deterioration due to aging [17], and perimenopause can be the "critical window" for opportunity in neuroprotection with steroids. The perimenopausal transition might also represent a "window of opportunity" to prevent age-related neurological diseases [10, 18, 19].

2. Hormonal and genetic data on perimenopausal neuroaging

The data of this chapter are regarding brain aging in perimenopause—a part in woman's reproductive life, systematized in the stages of reproductive aging (STRAW) [20].

Menopausal transition starts with the variation of cycles duration and ends with the last period (recognized only after 12 months of amenorrhea), natural menopause at the average age 51 years, premature menopause [premature ovarian failure (POF)] before 40 years, and early menopause between 40 and 45 years [21, 22]. Women with POF have been reported to have more anxiety, depression, somatization, sensitivity, hostility, and psychological distress than women with normal ovaries [23]. Perimenopause or "near menopause" starts from the stage −2 of menopausal transition and ends at 12 months after last menstruation, may be of 10–15 years. During this period, there are important variations of sex steroids, summarized by low ovarian inhibin [24], which in turn reduces the restraint on both the hypothalamus and pituitary gland, and results in elevated pituitary gonadotropin FSH, increased also by the hypothalamic gonadotropin-releasing hormone (GnRH). During the late menopause transition and a part of perimenopause, despite occasional episodes of normal cycling, women are exposed to periods of estrogen withdrawal, fewer ovulatory cycles, and prolonged hypogonadism, ultimately leading to the last menstrual period, after which is an elevated level of gonadotrophin secretion (only tonic, not phasic) [25]. During this phase, besides the low ovarian E2 and progesterone, there are productions of androgens and growth factors, which will decline in future years of postmenopause [26]. The ovaries are stimulated during menopausal transition and early postmenopausal years by gonadotropins, but the pulsatile GnRH pattern is different in different species before reproductive failure. It is a decrease of GnRH gene expression in many middle-aged rats [27], and an increase in perimenopausal rhesus monkeys [28].

Premature menopause/early menopause can be spontaneous or induced; after medical interventions such as chemotherapy/radiotherapy or surgery. The most common cause of premature/early menopause is bilateral oophorectomy with/without hysterectomy. Primary ovarian failure (POF) may be a cause of early/premature menopause, for ischemic stroke [29], as for all cardiovascular diseases risks [30], and these conditions were first described as a cause of neurological disturbances in different European, North American, and Japanese populations [21, 31–33].

Bilateral oophorectomy at premenopausal ages is inducing drops of E2 and testosterone levels, by 40–50%, and an abruptly rise in FSH levels, the levels of androgen being lower than in natural menopause at ages of 65 years, when women in normal or in premature/early menopause continue to have some levels of androgens [34]. As it is shown in the **Table 1**, the hazard ratios reached statistical significance in cases with bilateral oophorectomy: at the

Adjusted odd ratio for dementia after unilateral oophorectomy			
Age at surgery (years)	Hazard ratio	CI 95%	P value
<43	1.74	0.97–3.14	0.06
43–48	1.68	1.06–2.66	0.03
>48	1.09	0.74–1.61	0.66
Adjusted odd ratio for dementia after bilateral oophorectomy			
<34	4.61	2.52–8.43	<0.0001
34–41	1.23	0.67–2.26	0.51
>41	1.50	1.05–2.13	0.03
Adjusted odd ratio for PD after bilateral oophorectomy			
<38	2.85	1.28–6.35	0.001
38–45	1.38	1.28–6.35	0.42
>45	1.38	0.92–3.03	0.09

Cases of cognitive impairment/dementia and Parkinson disease (PD) in women with unilateral (813) and bilateral (676) oophorectomy: For a nonmalignant disease, in Olmsted County, Minnesota (USA) during 1950–1987, followed up the death or the finish of study at 2001–2006 (Rocca et al. [32]).

Table 1. Utero-ovarian surgery and neurological disturbances in premenopause.

age < 34 years for dementia and <38 years for PD. Perimenopause is a "fragile" period in woman's life, comparable to the fragility of the adolescence, if we speak about "hormonal storms," but the hormonal pyramid is upside down, and more than these, the North American neurologists are considering perimenopause as a neurological transition state [35], because the characteristic symptoms regarding thermoregulation, sleep, circadian rhythms, and sensory processing are of neurological nature, besides the changes of cognitive function [36].

The central and peripheral hormonal changes in menopausal transition and perimenopause were assessed in many research centers from Western Europe [37], Australia [24, 38], North America [25], and besides these, the rat models on gene expression analyses demonstrated that there are two distinct aging programs: chronological and endocrine, regarding bioenergetic gene expression involved in brain metabolism and synaptic plasticity [39].

The endocrine transition marked by changing from regular to irregular menstrual cycles is characterized by the impairment of the energy metabolism, glucose hypometabolism, and chronic oxidative stress, which were demonstrated by gene expression in brain metabolism, mitochondrial function, and long-term potentiation. Rat model analysis on brain energetic metabolism in menopausal transition demonstrated that insulin/insulin-like growth factor 1 and adenosine monophosphate-activated protein kinase/peroxisome proliferator-activated receptor gamma coactivator-1-alpha (AMPK/PGC1α) signaling pathways are upstream regulators [39], and these pathways suggest the critical role of E2 in neuronal survival. E2 stimulates the mitochondrial sequestration of Ca^{2+} and protects neurons against adverse consequences of excess cytoplasmic Ca^{2+} and subsequent dysregulation of Ca^{2+} homeostasis, with concomitant preservation of mitochondrial respiratory capacity [40].

Genetic analyses demonstrated that the menstrual cycles acyclicity is accompanied by a rise in genes required for fatty acid metabolism, a decline of genes required for mitochondrial function, β-amyloid degradation, and neuroinflammation including increased number in microglia population in aging hippocampus [41], plus the shift of microglia activation with predominant production of inflammatory cytokines [42], and a higher basal level of complement cascade genes and interleukin 1 receptor-like 1 in women versus men [43].

There are neuroimmune modulation differences in normal memory processes and memory dysregulation, in the roles of cytokines, astrocytes, and microglia in females and males [44]. These differences are from early development and differentiation of the brain [5], making women's brain inherently vulnerable to neurodegenerative diseases, to a higher risk of mild cognitive impairment and AD in advanced ages [45] (though not all studies are in agreement on this point, [1]), and non-neurodegenerative cognitive impairments fact that drive to the deleterious/beneficial consequences for estrogen therapy. The metabolic and neuroinflammatory changes are connected *via* redox regulation during normal brain aging, and may be predictive for later-life vulnerability to hypometabolic conditions of AD [46].

There are new animal studies on female neuroaging, regarding the microglia involvement in neurogenesis [47], to innate immune system [48], being revealed the microglia sensome by direct RNA sequencing [49]. Molecular studies on mice aging [50] revealed a central role of gender in the transcriptomic response in hippocampal and cortex aging, demonstrating sexually divergent changes of neuroinflammation, mainly an increase of microglia-specific genes, and C1q protein expression of the complement system, in the activation of astrocytes, and in cytokine release and function in aging. C1qa induction is a driver of synapse loss with greater C1qa induction associated with poorer cognitive performance. It is considered that the age-related changes in inflammatory hippocampal genes amplified in women after estrogen failure may contribute to sex differences in age-related neurological diseases. There are classes of genes in which inductions and reductions in gene expression are acting synergistically in female aging hippocampus [50].

The rise of microglia-specific genes in aging females is interrelated to a significant decrease in the activation of two pro-neurogenesis pathways evident in aging hippocampus: Notch1 and Presenilin 1 and 2 (PSEN1 and PSEN2) regulated genes [51]: Notch1 is necessary for neural stem cell maintenance [52], the PSEN1 expression regulates neuroprogenitor cell differentiation [53], and the defects in PSEN1 expression are associated with the manifestation of AD in old age [54]. Another change of neuroinflammatory genes in aging women is that of Tyrobp known as TREM2, as a causal regulator in microglia-associated changes in AD [55], and its proper mechanism in AD etiology is still being determined [56].

3. Hypothesis on brain aging and neurodegeneration during perimenopause

The months/years of perimenopause represent an important moment during women's aging, when steroids and their receptors decline is evident in the hippocampal and cortical neurons, after estrogen exposure during the reproductive years. The estrogens decline is associated/acts

synergic to other factors as hypertension, diabetes, hypoxia/obstructive sleep apnea, obesity, vitamin B12/folate deficiency, depression, and traumatic brain injury to promote different pathological mechanisms involved in brain aging, memory impairment, and AD.

The Californian and Australian neuroscientists had shown that chronic cerebral hypoperfusion deprives the brain from its two paramount trophic substances, oxygen and glucose, and consequently, the brain suffers from synaptic dysfunction and neuronal degeneration/loss, leading to both gray and white matter atrophy. The magnetic resonance imaging of the head used in the North American studies from Kronos Early Estrogen Prevention Study (KEEPS) showed a brain volume decrease with an average of 0.30–0.35% per year, and an increase of 3.59–3.73% in the ventricular volumes in the first 18 months of menopause [57], with a regional reduction of volume, which is more important in the hippocampus [58].

There are two hypotheses regarding neurodegeneration in brain aging, connected to low energy fuel supply, glucose hypometabolism and its complications for normal functioning [59], and microglia activation with associated secondary effect. In these hypothetical conditions, there are sexually divergent differences in gene expression in aging brain with comparing the number of gene expression changes in both males and females, and separating gene expression profiles based on up or downregulation.

The first hypothesis regards to the deficiency in glucose availability and mitochondrial dysfunction well-known as hallmarks of brain aging, which are particularly accentuated in neurodegenerative disorders, and the shift from an aerobic glycolytic to a ketogenic phenotype of bioenergetic metabolism. The model on female rat brain aging revealed that bioenergetic decline is starting from perimenopausal transition, which is followed by the decrease of brain synaptic plasticity [39]. The mouse female transgenic model of familial AD revealed that ovariectomy induces a shift in fuel availability and metabolism in the hippocampus, with an increase of enzymes required for long-chain fatty acid and ketone body metabolism, to obtain brain energy [46, 60]. Glucose hypometabolism associated to cerebral hypoperfusion initiated with perimenopausal atherosclerosis [61], hypercholesterolemia, nitric oxide, and impairment of redox homeostasis is considered as the key pathophysiologic promoter of neurodegeneration [59], and the known differences in regional brain metabolism make some women prone to AD [62].

Posterior cingulated and prefrontal cortex, which closely resembles the hypometabolic profile of AD brains are the postmenopausal women's brain areas with reduced cerebral blood flow, with alteration of brain blood barrier glucose transport, and with significant decline in glucose metabolism [63].

It was demonstrated that brain aging is associated with a decrease of central insulin concentration [64–66], with an impairment of insulin receptor binding ability, resulting in an increase in deterioration of glucose homeostasis in the brain. Brain insulin resistance [67] is associated to peripheral insulin resistance–a typical feature of elder ages, associated to atherogenic dyslipidemia [65], and ET influences insulin resistance in medial prefrontal gyrus metabolism.

The second hypothesis is focusing on neuroinflammation specifically after low estrogen levels, connected to the shift of microglia activation, with the changing rate of microglia after

activation M1 (classical) to M2 (alternative) type [68] or it is a maladaptive microglia activation [69], or a shift from neuroprotection to neurotoxicity, underlining chronic neuroinflammation and parainflammation, which is different in women and men [70, 71]. The shift is connected to proinflammatory cytokines and oxidative-nitrosative stress, which plus elevated levels of complement pathway components and other immune factors plays a key pathophysiological role in promoting cognitive dysfunction by enhancing endothelin, Amyloid-β deposition, cerebral amyloid angiopathy, aberrant synapse elimination in the hippocampus [72], and blood-brain barrier disruption.

AD is characterized by the loss of neurons and synapses from the cerebral cortex and certain subcortical regions of the temporal and parietal lobes, and parts of the frontal cortex and cingulated gyrus [73], and accumulation of plaque made up of small peptides called β-amiloid (also written as A-beta or Aβ). β-amyloid is a fragment from a larger protein called amyloid precursor protein (APP), a transmembrane protein that penetrates through the neuron's membrane. The Italian studies from Florence have demonstrated that estradiol is restoring in menopause the neuroprotective gene, seladin-1 (for SELective Alzheimer's Disease INdicator-1), or the gene DHCR24, which is downregulated in AD [74]. This gene inhibits the activation of caspase-3, a key modulator of apoptosis, and the gene encodes 3β-hydroxysterol, which catalyzes the conversion of desmosterol into cholesterol, and an appropriate amount of membrane cholesterol plays a pivotal role to protect nerve cells against Aβ toxicity and counteracts the synthesis of Aβ in AD [75, 76].

Microglia, a type of glial cell derived from myeloid precursors in the bone marrow that populate the CNS during development, as well as a brain resident innate immune cell, is the first line of defense in the CNS, as a monitor/sensor of neuronal activity in normal brain [77], protecting the local environment against invading pathogens, helping recovery from injury, and also in synapse pruning and neurodevelopment [78]. It is crucial in clearing debris, apoptotic/necrotic cells, or products from necrotic cells, infiltration of infectious agents, mediating the brain's inflammatory and repair response to traumatic injury, stroke, or neurodegeneration [79]. It was suggested that age-dependent and senescence-driven impairments of microglia functions and responses play essential roles during onset and progression of neurodegenerative diseases as AD and PD, in which molecular changes on microglia senescence are similar [80]. The unique nature and developmental origin of microglia causing microglial self-renewal and telomere shortening led to the hypothesis that these CNS-specific innate immune cells become senescent [81]. There are two important characteristics of human brain microglia: their heterogeneity observed in brain regions, and their different sensitivity to aging; the microglia from cortex, basal forebrain, and hippocampus are more sensible [81].

Microglia is activated from its normal state of a functionally "resting" resident immune cell of the CNS, and upon activation, microglia may proliferate and undergo a morphological transformation from a ramified to amoeboid appearance, and movement to sites of injury or stress can occur along with a release soluble immune mediators [82]. The activated microglia are functioning like a phagocyte or macrophage, having toll-like receptors (TLRs), that recognize specific molecular patterns as complement, mannose, scavenger, C-type lectin, nucleotide-binding oligomerization domain-like, and this specific action of microglia is called autophagy.

The autophagy is crucial for neuronal health and survival, the delivery of toxic molecules and organelles from neuronal apoptotic cells to microglia lysosomes may be acutely and/or chronically dysregulated by senescence, affecting phagocytosis and inflammation-innate immune functions in all age-associated neurodegenerative diseases [83]. There are two phenotypes of activated microglia: M1 (the cells become more cytotoxic by releasing additional pro-inflammatory cytokines- TNF, Il-1β, Il-6, and free radicals [84]), and M2, which becomes more anti-inflammatory, by secreting anti-inflammatory cytokines and neurotrophic factors and helps repair local damage [82]. The mouse model on AD is showing a distinct shift in activated microglia phenotypes, that occurs between the beginning of Aβ pathology (alternative phenotype), and advanced stages (classical phenotype), the latter may cause disease-associated neuron loss.

In this context, there are comments/discussions on microglia: if it is a scapegoat, a saboteur, or something else. A multicenter research group has discovered the presence of microglia amylin receptors mediating Aβ inflammation and neurodegeneration on primary cultures of fetal human and rats microglia [84], these receptors being common to neurons and microglia. It was proposed a model of microglia activation for AD, and neuronal death, involving these receptors, microglia, neurons, inflammation, amyloid precursor protein, and Aβ (**Figure 1**).

The amylin receptors are increasing as microglia responds to inflammatory triggers, such as lipopolysaccharide, resulting in microglia activation. The interaction of Aβ with amylin receptors of the activated microglia leads to increased production and release of cytokines, which act directly on neurons to produce cell death, with additionally increased production of Aβ *via* processing the amyloid precursor protein. The Aβ interacts with neurons and microglia amylin receptors to produce cell death [84].

The microglia activation is *via* the release of ATP, neurotransmitters, growth factors or cytokines, ion changes, special of Ca^{+2} in the CNS environment, or loss of inhibitor molecules displayed by healthy neurons, or when microglia cells encounter molecules not normally found in the healthy CNS, as blood clotting factors, intracellular constituents released by necrotic cells (hypomethylated mammalian DNA, RNA), externalized phosphatidylserine on apoptotic cells, immunoglobulin-antigen complexes, opsonizing complement, abnormally folded proteins or pathogen-related structures. When microglia activation occurs, the activation is correlated to the severity degree of the stressor, being recorded the disruptions of microglia functions causing synaptic dysfunction and excess synapse loss early in abnormalities of learning and memory [77].

Being a debate about the initiator from the two hypotheses: first, the bioenergetic hypothesis based on mitochondrial dysfunction, and the second on the microglia activation as the driving force for neuroinflammation, which is "a lesson learned from microglia depletion models" [85], there are multiple evidences that these abnormalities exacerbate each other, and these mechanistic diversities have cellular redox dysregulation as a common denominator and connector [86]. According to these, one may consider a metabolic inflammatory axis during brain aging and in neurodegenerative diseases [42]. In conditions of hypoglycemia, lactate can serve as an auxiliary fuel by metabolism of glycogen stores to generate glucose and subsequently lactate; some studies revealed that glial cells are likely to produce lactate in excess to its utilization by neurons [46].

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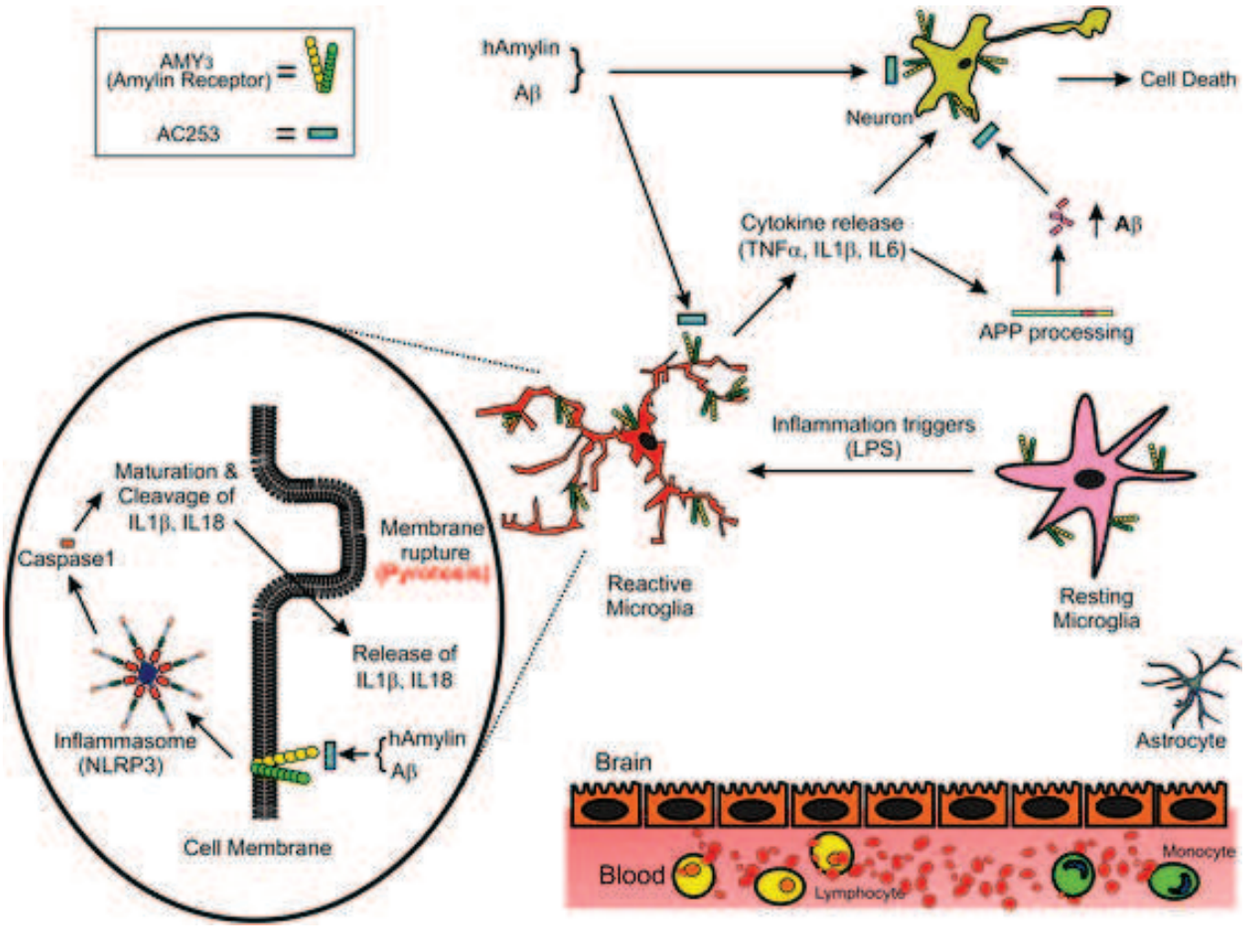

Figure 1. Model of neurodegeneration in AD proposed by Fu et al. [84]: Through the involvement microglia and neural amylin receptors in mediating the Aβ-induced neurodegeneration. *Legend:* The expression of amylin receptors of resting microglia, increased in response to inflammatory triggers like LPS, induces microglial cells activation. The interaction of Aβ with amylin receptors of the activated microglia leads to increased production and release of cytokines (TNF, Il-1β, and Il-6), which act directly on neurons to produce cell death and additionally augment the production of Aβ *via* processing of the amyloid precursor protein (APP). The Aβ, in turn, interacts with neuronal and microglial amylin receptors to produce cell death. Adapted from Fu et al. [84].

Neurological symptoms that emerge during perimenopause are indicative of disruption in multiple estrogen-regulated systems, and affect multiple domains of cognitive and memory functions [87].

Estrogens (special E2) are appreciated as a master regulator of bioenergetic systems in the body and brain [88].

The hypothesis on estrogen action or "healthy-cell bias" hypothesis [87, 89] is similar to the understanding of the different cardiovascular protective/harmful effects of estrogens at different women ages—protective before 60 years and harmful after 65 years. The protective effect of E2 is altered in the presence of the APOE4 genotype, which alters the response of microglia

and macrophages to 17β-E2 [90], and this fact may be an explanation of some studies showing better results with ET on memory recall in women aged around 70 and 20 years postmenopausal, if women have not demonstrated memory impairment [91].

It was demonstrated how during reproductive ages the estrogen-induced signaling pathways in hippocampal and cortical neurons converge upon the mitochondria to enhance aerobic glycolysis coupled to the citric acid cycle, mitochondrial respiration, and ATP generation, and in senescence when estrogens are missing, it is a chronic oxidative stress due to the shift from an aerobic glycolytic to a ketogenic profile/phenotype/ [35, 60], and this shift is preceded by the early, already mentioned decline in glucose transport and metabolism [46]. In mouse model, the mitochondrial bioenergetic deficit precedes AD [92]. The estrogen decline in perimenopause is associated to the decline in mitochondria bioenergetics and together with the shift to ketogenetic profile are steps to Aβ depositions in AD [93, 94]. Hexokinase, the first rate limiting step in glycolysis, interacts with mitochondria and prevents mitochondria-mediated apoptosis and through this mechanism, is promoting survival in neurons and other cell types [95], but AD patients exhibit declined hexokinase activity in the brain, cerebral microvessels, leukocytes, and fibroblasts.

Calcium dynamics play a pivotal and mandatory role in the estradiol-inducible cascade that leads to neurotrophic and neuroprotective benefit [89]. Dynamics of Ca^{2+} homeostasis are tightly regulated in healthy neurons and dysfunctional in degenerating neurons at elder ages.

The emergence of glucose hypometabolism, microglia activation, and impaired synaptic function in brain provide plausible mechanisms of neurological symptoms of perimenopause and can be predictive of later-life vulnerability to hypometabolic conditions such as AD. The alteration in the bioenergetic profile of the brain in the months/years of perimenopause may be an explanation for the controversies on estrogen therapy/hormone therapy divergent outcomes, beneficial [18, 19] or harmful (WHI Memory Study) effects on neural health, on memory and cognition [46].

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