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## Short review

## Unveiling FOXO3's metabolic contribution to menopause and Alzheimer's disease

Christopher O'Mahony, Oscar Hidalgo-Lanussa, George E. Barreto\*

Department of Biological Sciences, University of Limerick, Limerick V94 T9PX, Ireland

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## ABSTRACT

The increasing prevalence of Alzheimer's disease (AD) calls for a comprehensive exploration of its complex etiology, with a focus on sex-specific vulnerability, particularly the heightened susceptibility observed in postmenopausal women. Neurometabolic alterations during the endocrine transition emerge as early indicators of AD pathology, including reduced glucose metabolism and increased amyloid-beta ( $A\beta$ ) deposition. The fluctuating endocrine environment, marked by declining estradiol levels and reduced estrogen receptor beta ( $ER\beta$ ) activity, further exacerbates this process. In this context, here we explore the potential of forkhead box O3 (FOXO3) as a critical mediator linking metabolic disturbances to hormonal decline. We propose that FOXO3 plays a key role in the intersection of menopause and AD, given its dysregulation in both AD patients and postmenopausal women, modulating cellular metabolism through interactions with the AMPK/AKT/PI3K pathways. This relationship highlights the intersection between hormonal changes and increased AD susceptibility. This review aims to open a discussion on FOXO3's contribution to the metabolic dysregulation seen in menopause and its impact on the progression of AD. Understanding the functional role of FOXO3 in menopause-associated metabolic changes could lead to targeted therapeutic strategies, offering novel insights for managing for this condition.

## 1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease and one of the leading causes of dementia worldwide. According to the World Health Organization (WHO), over 55 million people are currently living with dementia, a number projected to rise to 150 million over the next three decades, with approximately 16.3 million cases anticipated in Europe alone (Nichols et al., 2022; Georges et al., 2020). Memory decline and cognitive deterioration are the hallmark symptoms of AD in the elderly population (De-Paula et al., 2012). Histopathologically, the disease is characterized by the accumulation of amyloid-beta ( $A\beta$ ) plaques and tau neurofibrillary tangles (NFT), which disrupt normal neuronal function, leading to synaptic loss and neuronal death (Breijyeh and Karaman, 2020). Recent epidemiological, neuroimaging, and neuropathological studies suggest that AD results from a complex interplay of environmental, lifestyle, and genetic factors (Weiner et al., 2010; Mayeux and Stern, 2012).

There are significant sex-based differences in the onset and progression of AD, with females being two to three times more likely to develop the disease despite having longer life expectancies (Association,

A.s, 2019; Mielke et al., 2014; Williams and Carter, 2009). In fact, females account for approximately two-thirds of AD cases (Association, 2022). Although the exact causes behind these sex-related disparities remain unclear, hormonal imbalances, particularly the decline in estrogen levels during menopause, and genetic factors, such as the higher prevalence of the APOE4 allele in females (Simpkins et al., 2012), may provide partial explanations. Notably, females undergoing menopause exhibit AD-like characteristics, including changes in brain metabolism, mild inflammation (Yasui et al., 2007), and reduced white matter volume, which may correlate with increased  $A\beta$  deposition compared to premenopausal females and age-matched males (Mosconi et al., 2021; Mosconi et al., 2017a; Mosconi et al., 2017b). During menopause, the reduction in estradiol levels and diminished estrogen receptor beta ( $ER\beta$ ) activity (Shults et al., 2015; Yamaguchi and Yuri, 2014; Yamaguchi-Shima and Yuri, 2007) can promote a pro-inflammatory environment (de Rivero Vaccari et al., 2016), leading to mitochondrial dysfunction and metabolic disturbances (Gonzalez-Giraldo et al., 2019; Hidalgo-Lanussa et al., 2018; Avila-Rodriguez et al., 2016). These metabolic changes are thought to contribute to increased  $A\beta$  accumulation (Mosconi et al., 2017a; Mosconi et al., 2017b), potentially

\* Corresponding author.

E-mail address: [George.Barreto@ul.ie](mailto:George.Barreto@ul.ie) (G.E. Barreto).<https://doi.org/10.1016/j.exger.2025.112679>

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accelerating cognitive decline (Zhang et al., 2022; Liu et al., 2021). However, further research is needed to investigate how these factors, in combination with environmental and social stressors, influence the onset and progression of the disease.

One key protein that may play a role during menopause and contribute to the elevated incidence of AD in women is Forkhead box O3 (FOXO3). Alterations in FOXO3 expression have been observed in AD patients (Pradhan et al., 2020), and it is closely linked to estradiol in regulating longevity and cellular metabolism (Sanese et al., 2019). This connection suggests that FOXO3 could serve as a metabolic link between AD and menopause. This review aims to explore the potential role of FOXO3 in the progression of AD, highlighting its interactions with hormonal and metabolic pathways. Understanding the underlying causes of sex-specific alterations in AD and developing tailored treatments for both sexes could significantly enhance the quality of life for those affected by this devastating condition.

## 2. Sex differences in AD

Epidemiological and observational studies consistently show that females have a higher likelihood of developing AD (Mielke et al., 2014) compared to age-matched males. While various biological factors contribute to this sex difference (Norton et al., 2014), other studies suggest that social determinants, such as education levels (Sando et al., 2008), socioeconomic status (Ferretti et al., 2018), and longevity (Hebert et al., 2001) may also play a significant role in the observed sex disparity. Additionally, factors such as inflammation, menopause, mood disorders, genetic predisposition, and brain structure abnormalities (Fisher et al., 2018) are believed to contribute to the higher prevalence of AD in females.

### 2.1. Neuroanatomical and genetic alterations

Post-mortem studies have revealed that females with AD, compared to age-matched males, exhibit higher levels of A $\beta$  plaques and NFT formation (Oveisgharan et al., 2018). This highlights key sex differences in AD pathology, particularly the increased rate of brain atrophy observed in females with mild cognitive impairment (MCI) or AD (Corder et al., 2004). This has been confirmed in animal models such as the Swedish mutant amyloid precursor protein (APP) mice (APP695SWE), where female mice exhibit earlier accumulation of A $\beta$  compared to males between 8 and 12 months of age (Callahan et al., 2001). By 15 months, female mice have three times as many amyloid plaques as their male counterparts, with A $\beta$ 40 being the predominant form. These findings emphasize the importance of exploring sex disparities in AD, which could guide the development of sex-specific therapeutic strategies.

Sex differences have also been observed in the effects of the apolipoprotein allele 4 (APOE4) allele. Females carrying the APOE4 allele have a two-fold higher risk of developing AD compared to their male counterparts with the same genetic variant (Payami et al., 1996). APOE4 is recognized as the most significant genetic risk factor for late-onset AD, found in more than half of all AD cases (Ward et al., 2012; Yamazaki et al., 2019). The presence of this allele is associated with an earlier onset of the disease, greater A $\beta$  deposition, neuroinflammation, impaired glucose metabolism, and synaptic degeneration (Yamazaki et al., 2019).

### 2.2. Neuroinflammation and oxidative stress

Neuroinflammation plays a crucial role in the pathogenesis of AD. A $\beta$  plaques and NFTs interact with inflammatory processes, triggering an immune response that exacerbates the disease (Thakur et al., 2023; Sobue et al., 2023). In postmenopausal women, the depletion of ovarian hormones may worsen autoimmune diseases and increase inflammation (McCarthy and Raval, 2020). Furthermore, pro-inflammatory cytokines

such as IL-6 and TNF- $\alpha$  are elevated after menopause, further increasing the vulnerability of females to chronic inflammation and immunological diseases (Kim et al., 2012).

Oxidative stress, defined as an imbalance between oxidants and antioxidants leads to cellular damage, is another major contributor to neurodegenerative diseases, including AD (Kim et al., 2015). Studies comparing the brains of aged females and aged-matched males have shown stronger indicators of oxidative stress in females, suggesting an increased vulnerability to oxidative damage (Claudia Camelia Calzada and Jiménez, 2013; Kander et al., 2017; Schuessel et al., 2004). Previously, a study by Mandal et al. (2012) aimed to assess sex differences in brain glutathione (GSH) levels, an important antioxidant involved in combating oxidative stress. This study, which included 85 participants (healthy individuals and those diagnosed with MCI and AD), found that females with MCI and AD exhibited significantly lower GSH levels (Mandal et al., 2012). In contrast, healthy individuals showed the highest GSH levels in the parietal cortex. This decline in GSH levels in MCI and AD patients highlights the role of oxidative stress in neurodegeneration, underscoring the need to explore effective strategies to manage and treat oxidative stress, particularly in specific brain regions. While this review's goal is to explore the intersection of menopause, AD and FOXO3 in relation to metabolism, it is not intended to fully focus on neuroinflammation, as comprehensive reviews on this topic have been published recently (McCarthy and Raval, 2020; Breeze et al., 2024).

## 3. Impact of hormonal changes: menopause

Aging is characterized by a progressive decline in physiological functions, including significant alterations in the endocrine system. Recent research has drawn attention to the relationship between endocrine aging and the onset and progression of neurodegenerative diseases, among female populations (Scheyer et al., 2018; Jett et al., 2022). One of the most notable endocrine changes associated with aging is the menopausal transition, which has profound effects on brain function and metabolic health (Mosconi et al., 2021). Menopause marks the permanent cessation of menstrual cycles due to the depletion of ovarian follicular activity, occurring either naturally or following surgical intervention.

Menopause is primarily driven by the depletion of ovarian follicles (Nejat and Chervenak, 2010), which are formed before birth and gradually decrease throughout a female's reproductive years. This decline typically occurs between the ages of 45 and 55 (Nejat and Chervenak, 2010; Davis et al., 2015), resulting in a reduction in egg quality and, eventually, the cessation of ovulatory cycles. This process begins in the 40s and progresses through distinct stages of the menopausal transition. Perimenopause, the early stage of this transition, is characterized by irregular menstrual cycles and hormonal fluctuations (Broekmans et al., 2009). As follicular depletion progresses, menstrual cycles become more irregular, leading to the late stage of menopause and the final menstrual period (Broekmans et al., 2009). Menopause is formally confirmed after 12 consecutive months without menstruation, indicating near-total follicular depletion. Typically occurring between the ages of 45 and 55, the entire menopausal transition spans approximately 14 years and represents a critical period of endocrine aging (Harlow et al., 2012).

The menopausal transition represents a crucial period in women's life, marked by significant hormonal shifts and a decline in ovarian function. One of the most prominent hormonal changes is the reduction in estradiol levels, which profoundly impacts brain structure, connectivity, and, mainly, energy utilization. This decline in estradiol is also associated with increased neuroinflammation and oxidative stress, both of which are key factors in AD (Mosconi et al., 2021; McCarthy and Raval, 2020). The connection between hormonal fluctuations during the menopause and alterations in brain functions shows the intimate relationship between hormonal aging and neurodegeneration. These changes warrant further investigation to better understand their role in neurodegenerative conditions to identify potential strategies for

preventing or managing these disorders.

#### 4. Estradiol, receptors, and neuroprotection

Estradiol, a vital sex hormone and steroid, performs a wide range of physiological functions beyond its role in shaping female reproductive characteristics. These functions include intracellular signalling, transcriptional regulation, anti-inflammatory responses, and metabolic homeostasis (Azcoitia et al., 2019; Hidalgo-Lanussa et al., 2020; Mohajeri et al., 2019; Barreto et al., 2021; Martin-Jimenez et al., 2019; Giatti et al., 2019; Vega-Vela et al., 2017; Acaz-Fonseca et al., 2016). Estradiol exerts these effects through its interaction with estrogen receptors (ERs), namely estrogen receptors alpha (ER $\alpha$ ), beta (ER $\beta$ ), and G Protein-Coupled Estrogen Receptor 1 (GPER1). These receptors mediate both genomic and non-genomic outcomes (Chen et al., 2022), allowing estradiol to act across various tissues, including the brain, a steroidogenic organ with high metabolic demands. The complex mechanism by which estradiol influences these processes involve the interaction between these ERs and distinct molecular sites, such as DNA and ligand binding domains (Chen et al., 2022; Eyster, 2016).

ER $\alpha$  (66 kDa) and ER $\beta$  (59 kDa) are critical mediators of estradiol's tissue-specific effects. ER $\alpha$  is predominantly expressed in reproductive organs, but also appears in non-reproductive tissues, including the brain, where it contributes to regulating energy metabolism (see a recent review (Rasic-Markovic et al., 2024)). ER $\beta$ , on the other hand, is broadly distributed, present in male reproductive tissues, the central nervous system (CNS), and other tissues (Hamilton et al., 2017). Within the brain, ER $\beta$  is particularly important for regulating mitochondrial bioenergetics, including oxidative phosphorylation and ATP production (Gonzalez-Giraldo et al., 2019; Hidalgo-Lanussa et al., 2018; Klinge, 2020). Studies have linked estrogen receptor activity to enhanced mitochondrial functions in neurons (McCarthy and Raval, 2020; Osterlund and Hurd, 2001), highlighting its contribution to maintaining cellular energy homeostasis and reducing oxidative stress.

Aging is also associated with a significant decline in the expression of estrogen receptors, particularly ER $\beta$ , which is markedly reduced in the hippocampus and neuronal mitochondria of female brains affected by AD (Rasic-Markovic et al., 2024; Hamilton et al., 2017; Klinge, 2020). This decline may correlate with decreased mitochondrial efficiency, impaired glucose metabolism, increased oxidative damage and reduced neuronal metabolic resilience. Such metabolic disruptions are thought to contribute to the increased vulnerability of postmenopausal women to AD. Understanding the role of estradiol and its receptors in brain metabolism provides valuable insights into their neuroprotective functions, with a key goal of developing targeted interventions to modulate ER activity, mitigate metabolic dysfunction, and reduce AD risk in aging females.

##### 4.1. Estradiol's neuroprotective role in Alzheimer's disease

Considerable research has been devoted to exploring the involvement of estradiol in AD and cognitive decline, given to its critical role in maintaining neural integrity. Recent reviews have underscored the importance of this topic (Jett et al., 2022; Barth et al., 2023; Sayfullaeva et al., 2024). Briefly, studies using neuronal models have demonstrated estradiol's neuroprotective properties, particularly in protecting against A $\beta$  neurotoxicity, oxidative metabolic stress, and apoptosis (Li and Wang, 2017; Mendelowitsch et al., 2001; Sudo et al., 1997; Xu et al., 2006), thereby enhancing neuronal resilience.

Estradiol's protective effects are not limited to passive defense mechanisms; it actively engages in pro-survival signalling pathways involving BDNF, FOXO3, MAPK and cAMP, which regulate neural network survival and function (Simpkins et al., 2012; Hara et al., 2015; Scharfman and MacLusky, 2006). Evidence linking cognitive decline to decreased levels during the menopausal transition (Ramli et al., 2023; Karamitrou et al., 2023; Stefanowski et al., 2023; Bove et al., 2014;

Kantarci et al., 2018), highlights the potential of estradiol administration to preserve cognitive function (Sherwin, 1997; Phillips and Sherwin, 1992). Animal studies have further shown that estradiol depletion in ovariectomised animals increases brain susceptible to damage and reduces cognitive resilience (Park et al., 2006; Alkayed et al., 1998). In brain mitochondria, estradiol acts as a potent antioxidant, enhancing the brain's antioxidant defenses and preventing oxidative damage that contributes to neurodegeneration (Vina and Borras, 2010; Borras et al., 2003).

It is well-established that estradiol could improve cognitive function. Transgenic mouse studies have provided additional insights into its role in AD pathology. For instance, Yue et al. (2005) demonstrated that estradiol-deficient APP23 transgenic mice exhibited increased A $\beta$  levels and decreased A $\beta$  clearance compared to estradiol-intact APP23 mice. These findings suggest that estradiol depletion promotes A $\beta$  deposition, a hallmark of AD, reinforcing the crucial role of this hormone in mitigating disease progression (Xu et al., 2006). Furthermore, estradiol significantly influences glucose metabolism, enhances insulin secretion, and improves mitochondrial function, all of which are critical for maintaining neuronal health and addressing AD-related metabolic impairments (McCarthy and Raval, 2020; Bian et al., 2019; Mosconi et al., 2008) (Fig. 1). With this in mind, the next section of this review shifts focus onto the intricate relationship between cellular energetics, particularly glucose metabolism, in the context of menopause and AD.

#### 5. Bioenergetic changes: a link between menopause and Alzheimer's disease

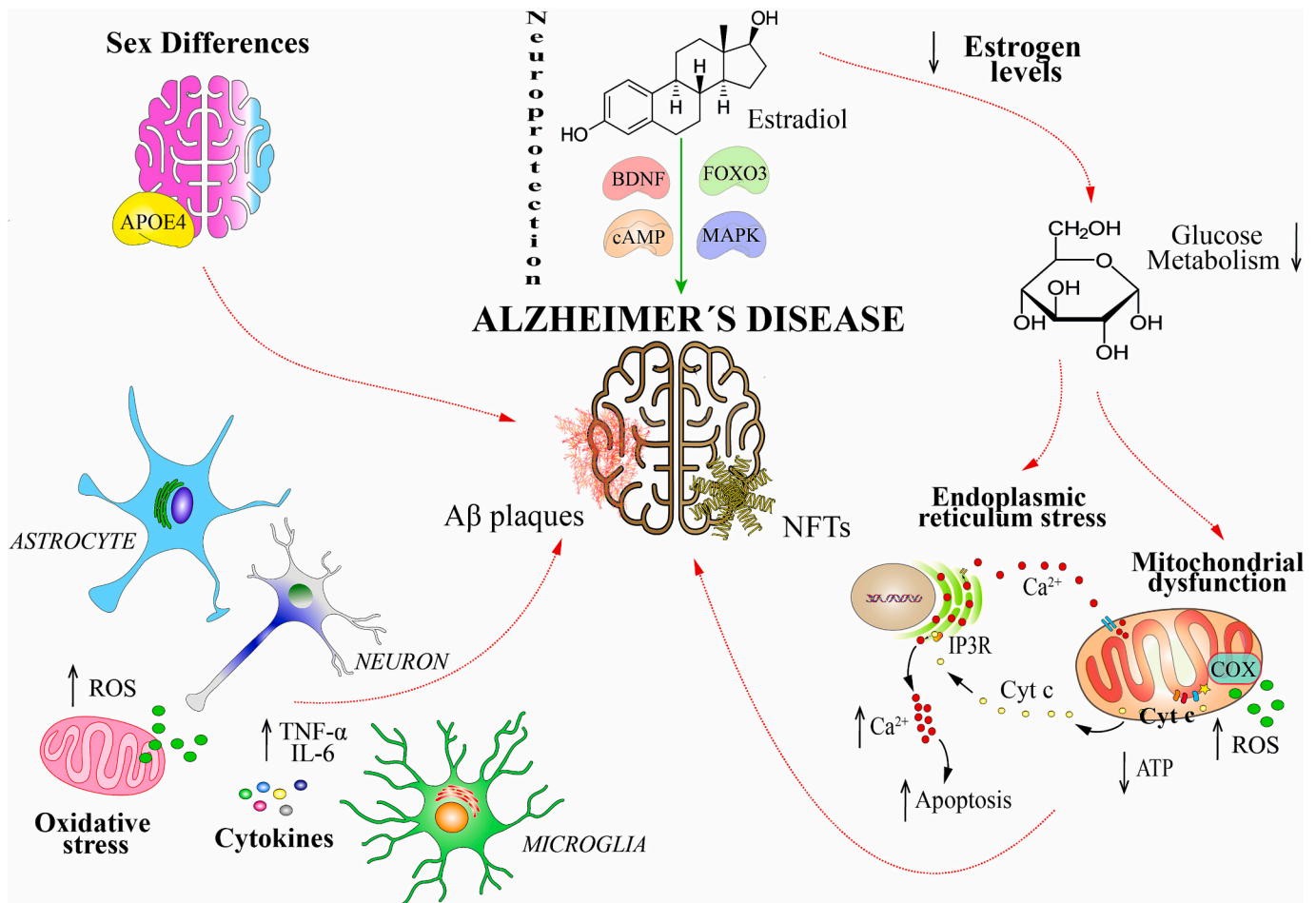
##### 5.1. Brain glucose metabolism

The brain, despite constituting only about 2 % of total body weight, accounts for approximately 20 % of the body's total energy expenditure (Borras et al., 2003), highlighting its high metabolic demand. This substantial energy requirement is largely met through glucose metabolism, making the brain highly vulnerable to disturbances in bioenergetics, as glucose deprivation significantly impacts mitochondrial function in brain cells (Avila-Rodriguez et al., 2016; Avila Rodriguez et al., 2014; Baez et al., 2017; Vesga-Jimenez et al., 2019). Any disruption in glucose metabolism or mitochondrial efficiency can significantly impair the function of both neuronal and glial cell function (Costantini et al., 2008).

Hormonal changes during menopause affect bioenergetic functions, with estradiol playing a key role in regulating cerebral glucose metabolism. Estradiol enhances glucose transport, glycolysis, and oxidative phosphorylation in neuronal mitochondria (McCarthy and Raval, 2020; Park et al., 2006). As estradiol declines, there is a corresponding reduction in glucose uptake, as evidenced by fluorodeoxyglucose-positron emission tomography (FDG-PET) studies. These studies reveal hypometabolism in key brain regions, such as the hippocampus and posterior cingulate cortex, which are particularly vulnerable to AD pathology (Crane et al., 2013; Kapogiannis and Mattson, 2011; Langbaum et al., 2010; Marcus et al., 2014). Furthermore, mitochondrial dysfunction linked to estradiol deficiency exacerbates oxidative stress and impairs ATP production, which ultimately affects synaptic activity and neuronal resilience. Collectively, these findings suggest that menopause-induced disruptions in glucose metabolism and mitochondrial efficiency create a bioenergetic environment that may accelerate the progression of AD (Yao and Brinton, 2011; Goyal et al., 2017).

##### 5.1.1. Glucose hypometabolism in AD

A growing body of research, including genomic analysis of animal or post-mortem human brains, in vitro cell models, and neuroimaging consistently supports the hypothesis of glucose hypometabolism (Hauptmann et al., 2009; Lustbader et al., 2004; Wang et al., 2020a; Croteau et al., 2018; Winkler et al., 2015). Using FDG-PET, researchers have observed significant reductions in metabolic activity in cortical



**Fig. 1.** Influence of menopause on the progression on Alzheimer's disease. The menopausal phase is characterized by a decline in endogenous estradiol levels, which predisposes females to neurodegenerative conditions such as Alzheimer's disease. This hormonal decrease is linked to disrupted cellular homeostasis, driven by metabolic perturbations such as reduced glycolytic metabolism, elevated oxidative stress in mitochondria, endoplasmic reticulum stress, and the activation of proinflammatory molecules alongside increased glial reactivity. Estradiol plays a neuroprotective role by activating multiple mechanisms including FOXO3, MAPK and the release of neurotrophic factors like BDNF, thereby mitigating these pathological effects.

regions associated with AD, such as the hippocampus, in patients with AD compared to age-matched cognitively intact controls (Crane et al., 2013; Kapogiannis and Mattson, 2011; Langbaum et al., 2010; Marcus et al., 2014). Moreover, emerging research suggests that menopause impacts glucose uptake and glycolytic enzyme activity, particularly platelet cytochrome oxidase (COX), reflecting glucose deregulation patterns similar to those seen in AD (Mosconi et al., 2017a). In addition, studies of individuals with mild cognitive impairment (MCI) show early signs of glucose hypometabolism (Drzezga et al., 2005), further supporting the idea that this metabolic dysfunction begins early in the disease process.

As previously mentioned, menopause triggers a decline in glucose metabolism, prompting cellular adaptations to meet energy demands (McCarthy and Raval, 2020). This metabolic shift, from glucose metabolism to lipid or ketone utilization, is also a prominent feature of AD pathology (Wang et al., 2020b). The hypometabolic state observed during the perimenopause period and in AD is frequently accompanied by an increase in oxidative stress, endoplasmic reticulum (ER) stress, and apoptosis, all of which contribute to neurodegeneration (Lin and Beal, 2006; Burté et al., 2015). Consequently, these metabolic disruptions may likely establish a link between the menopause and the onset of AD, emphasizing the role of compromised bioenergetics in AD progression (Wang et al., 2020a).

### 5.2. Impaired mitochondria in AD resembles that occurring during menopause

As previously stated, the decline in glycolytic metabolism observed in AD can be attributed to bioenergetics dysfunction, a condition that may be further exacerbated during menopause. Bioenergetics refers to the processes by which energy is generated, stored, and utilized within organisms, with mitochondria playing a central role in this paradigm (Vakifahmetoglu-Norberg et al., 2017). These organelles are essential for maintaining cellular homeostasis, as their primary function is the production of ATP through oxidative phosphorylation (Lin and Beal, 2006). When mitochondrial function becomes compromised, as seen in both AD and menopause, it leads to energy deficits, oxidative damage, and other cellular dysfunctions. Previous proteomics studies from our group show that gonadal hormone deprivation in castrated 2-month-old animals leads to alterations in oxidative phosphorylation, respirasome proteins, and calcium signalling pathways crucial to neurodegeneration and among the most highly regulated clusters (McGovern et al., 2022; McGovern et al., 2024). This is particularly important, as female cells (e.g. astrocytes) exhibit more pronounced mitochondrial ROS stress, rather than cytosolic ROS, compared to male counterparts when challenged with inflammatory damage (Hidalgo-Lanussa et al., 2024). Similarly, in AD, mitochondrial function manifests through disturbances in the electron transport chain and a decrease in ATP production, and the subsequent oxidative damage to cellular components, all of which are

crucial to understanding the pathophysiology of the disease (Swerdlow, 2011). Additionally, alterations in calcium balance and the activation of pro-apoptotic signalling contribute to cell death and inflammation (Nicolson, 2014; Norat et al., 2020), further aggravating the energetic and metabolic dysregulation within the brain.

There is no doubt that mitochondrial dysfunction is a hallmark of AD pathology (Gorham et al., 2023; Sousa et al., 2023; Barreto, 2023), with one of the key contributors being the accumulation and translocation of amyloid- $\beta$  (A $\beta$ ) peptides into mitochondria. This disrupts mitochondrial electron transport chain (Hirai et al., 2001), leading to a decreased mitochondrial membrane potential (Caspersen et al., 2005) and impairing ATP synthesis. A $\beta$  also interferes with mitochondrial dynamics, including the processes of fission and fusion, and alters calcium regulation. This can promote mitochondrial permeability transition pores, ultimately reducing ATP synthesis and triggering apoptosis (Du et al., 2008). Chronic inflammation, a key feature of AD, also exacerbates immune system responses (Pfeilschifter et al., 2002; Giuliani et al., 2001), which in turn contributes to further damages mitochondria.

Similar mitochondria dysfunction is observed during the menopausal transition, where reduced estradiol levels are linked to a decline in mitochondrial respiration (Yao et al., 2010; Ding et al., 2013). This decline may be partially attributed to reduced ER $\beta$  activity within mitochondria (Shults et al., 2015; Yamaguchi and Yuri, 2014; Yamaguchi-Shima and Yuri, 2007; Yang et al., 2004), as ER $\beta$  plays a crucial role in mitochondria function. As estradiol levels gradually decrease, there is a reduction in mitochondrial efficiency, which mirrors the mitochondrial dysfunction observed in AD. This connection further demonstrates the strong link between menopause-associated metabolic changes and the pathophysiology of neurodegenerative diseases.

### 5.3. Metabolic shift to lipid metabolism and cellular reprogramming

The brain's metabolic landscape faces significant challenges when glucose hypometabolism occurs, as the normal energy supply from glucose becomes compromised. Diminished glucose uptake and metabolism in brain cells (Marcus et al., 2014) can lead to metabolic dysfunction and energy shortages, particularly in critical brain regions that are more susceptible to neurodegeneration. In response to these deficits, brain cells exhibit remarkable adaptability, shifting to alternative fuel sources, such as lipids or ketones (Croteau et al., 2018; Cunnane et al., 2020).

Lipids, stored as triglycerides and phospholipids in the brain, represent significant energy reserves. These lipids undergo lipolysis, releasing fatty acids that can be taken up by brain cells. Once inside the cells, fatty acids are metabolized via beta-oxidation within mitochondria, converting lipids into ATP (Bogie et al., 2020). This metabolic adaptation serves as a vital alternative energy source, enabling cells to maintain their cellular activities even under glucose-deficient conditions. However, this shift to lipid metabolism, while helpful for sustaining cellular energy, is less efficient and slower than glucose metabolism (Cunnane et al., 2016), especially for brain functions that are highly-glucose dependent. As a result, relying predominately on lipids may not fully meet the energy demands of the brain, particularly in regions traditionally dependent on glucose. This may render these areas more vulnerable to dysfunction and neurodegeneration.

This shift in fuel utilization is part of a broader reprogramming of brain cell metabolism. However, the focus of this review is specifically on the hormonal regulation of cellular energy pathways. In this context, the protein FOXO3 emerges as a key player, potentially bridging as the hormonal changes occurring during menopause and the metabolic pathways implicated in AD. FOXO3 has been shown to regulate various aspects of cellular metabolism, stress response, and longevity, suggesting that it may be a crucial mediator in the metabolic impairment in both menopause and AD.

## 6. FOXO3 – a possible link between menopause and Alzheimer's disease

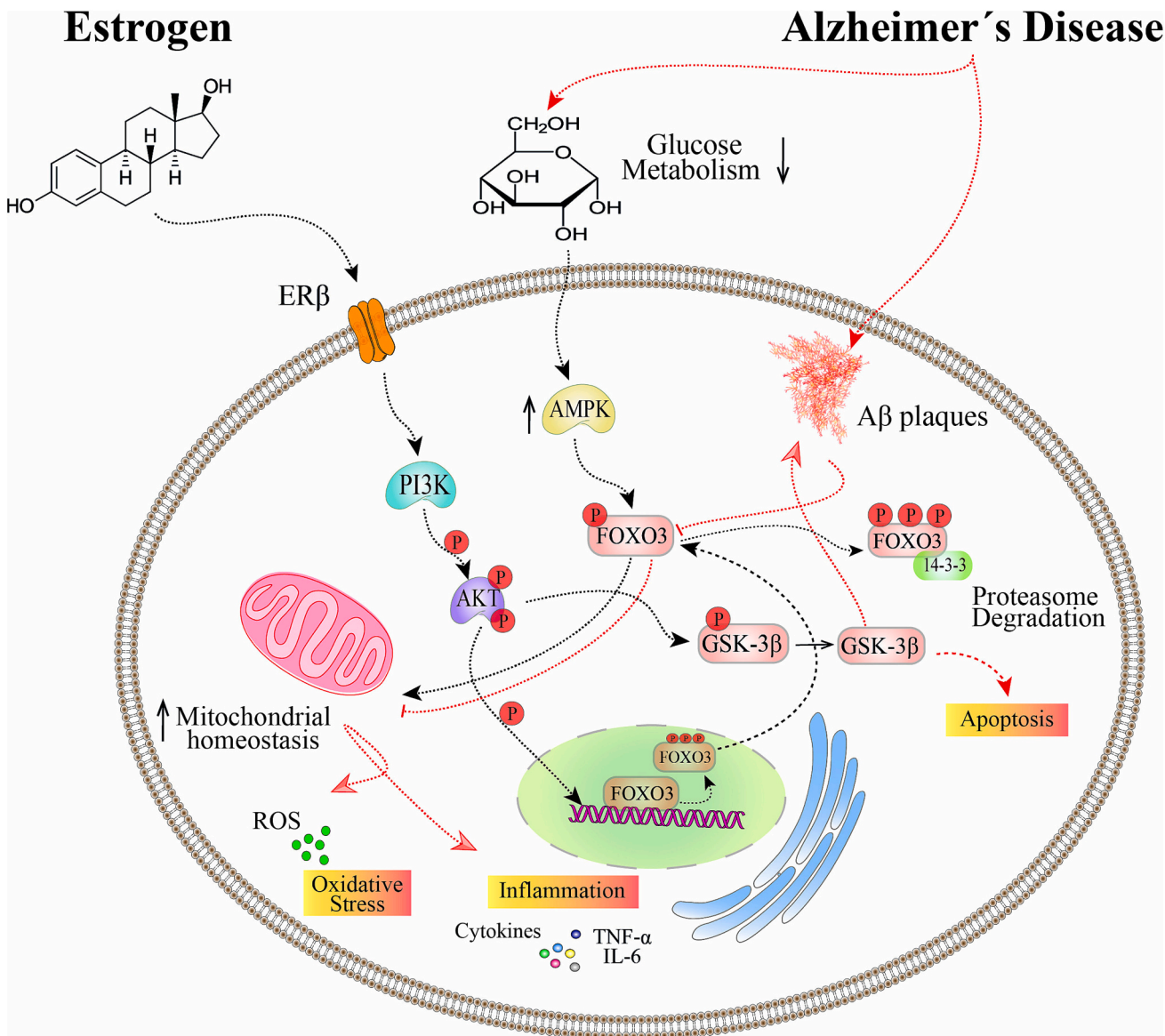
FOXO3 regulates the expression of key metabolic proteins such as mTORC1, antioxidants like catalase and manganese-superoxide dismutase (MnSOD) (Li et al., 2006; Olmos et al., 2009), and the autophagy-related ATG12, BNIP3, ATG8 (Mammucari et al., 2007). These multifaceted functions allow FOXO3 to preserve cellular integrity and counteract the adverse effects of aging and neurodegeneration (Chang et al., 2023). The FOXO family was first identified in the nematode *Caenorhabditis elegans*, where they were found to be involved in cellular stress responses, cell viability, and lifespan extension (Morris et al., 2015). Subsequent studies in higher organisms, including *Drosophila melanogaster* and mammals have expanded this understanding. Unlike invertebrates, which generally have a single FOXO protein (DAF-16), mammals possess four FOXO isoforms: FOXO1, FOXO3, FOXO4, and FOXO6 (Morris et al., 2015; Du et al., 2021; Kramer et al., 2003; Spellberg and Marr 2nd, 2015).

Recent research has shed new light on the complex interactions between estrogen signalling and FOXO3, with significant implications for cellular function and the pathophysiology of menopause and AD (Fig. 2). Interestingly, ER $\beta$  has emerged as a key regulator of FOXO3 activity. Dey et al. (Dey et al., 2014a) demonstrated that overexpression of ER $\beta$  in PC3 and 22Rv1 cells, combined with treatment using 3 $\beta$ -Adiol (a natural ER $\beta$  ligand), significantly increased apoptosis rates through FOXO3 activation. Conversely, ER $\beta$  knockdown via siRNA reduced FOXO3 levels and diminished the ligand's effects on the pro-apoptotic p53 upregulated modulator of apoptosis (PUMA) (Dey et al., 2014b). Mechanistically, two estrogen response elements (EREs) and an AP1 domain have been identified upstream of the FOXO3 gene, suggesting transcriptional regulation by ER $\beta$ . In addition, an in silico analysis of the FOXO3 SNP rs2802292 identified a transcription response element for ES1 (estrogen receptor alpha) (Grossi et al., 2018), highlighting the broader involvement of estrogen receptors in FOXO3 regulation. Studies further indicate that estradiol activation of ER $\beta$  enhances FOXO3 expression and function in females (Morelli et al., 2010), contributing to improved cellular stress response, increased longevity, and neuroprotection. The interaction between ER $\beta$  and FOXO3 offers a promising avenue for understanding sex differences in AD. FOXO3 may act as a mediator of the neuroprotective effects of estradiol, linking hormonal regulation to cellular stress pathways and neurodegenerative progression.

### 6.1. Mechanisms of FOXO3 regulation: shared pathways between AD and menopause

FOXO3 primarily functions in response to cellular stress rather than maintaining normal cellular homeostasis (Morris et al., 2015). Its activity is intrinsically regulated by several signalling pathways such as PI3K-AKT and AMPK, which influence FOXO3 through post-translational modifications, particularly phosphorylation. The PI3K-AKT-FOXO3 axis is pivotal in FOXO3 regulation. For instance, AKT, downstream of PI3K and upstream of FOXO3, is crucial in this regulation. Upon activation, AKT translocates to the nucleus, where it phosphorylates FOXO3 at multiple sites, including Ser253, Ser315 and Thr32. This phosphorylation promotes FOXO3 to bind to 14-3-3 proteins, resulting in its translocation to the cytoplasm, rendering it inactive (Tzivion et al., 2011; Link, 2019). Stimuli such as insulin, growth factors, and ER $\beta$  agonists activate the PI3K-AKT pathway, reflecting the dynamic regulation of FOXO3 (Yang et al., 2019; Maria Kristina and Anna, 2018).

Interestingly, sex differences in FOXO3 expression and activity have been observed. Female mice exhibit higher levels of phosphorylated (inactive) FOXO3 compared to males, indicating reduced nuclear FOXO3 (de Mello et al., 2020) and diminished transcriptional activity of its stress and metabolic-related targets. Estradiol appears to modulate this pathway. In ovariectomized female rats subjected to middle cerebral



**Fig. 2.** Impact of estradiol on FOXO3 mechanistic actions in Alzheimer's disease (AD). Estradiol interacts with its receptors to activate the PI3K-AKT signalling pathway. This activation promotes the phosphorylation of AKT, which, in turn, regulates FOXO3 activity through specific post-translational modifications at specific sites. Phosphorylated FOXO3 translocates to the cytoplasm via binding to the 14.3.3 protein, modulating its functional role. FOXO3 emerge as a potential interaction between menopause and AD, where it regulates metabolism, mitochondrial integrity, and attenuates apoptosis, addressing the detrimental effects of reduced glycolytic metabolism observed in AD pathology.

artery occlusion (MCAO), estradiol treatment prevented reductions in AKT and FKHL1 (aka FOXO3) phosphorylation and promoted the interaction of pFKHL1 with 14-3-3 (Won et al., 2006). Similar results were observed in a global ischemia model, where estradiol prevented AKT and FOXO3 dephosphorylation induced by injury and caspase-3 activation, promoting neuronal survival (Jover-Mengual et al., 2010). These findings suggest estradiol's neuroprotective role via enhanced PI3K-AKT-FOXO3 signalling.

FOXO3 is also critical in regulating mitochondrial health. Du et al. (2021) showed a decrease in FOXO3 expression in the cerebral cortex of aged animals, with increased translocation of FOXO3 to the cytoplasm in primary astrocytes following insulin administration or PI3K inhibition with LY294002, compared to primary neurons. Primary astrocytes from FOXO3 conditional knock-out mice exhibited altered mitochondrial function, such as reduced ATP levels and diminished mitochondrial membrane potential, a key indicator of mitochondrial health. The metabolic changes observed in FOXO3-deficient astrocytes led to

diminished phagocytic activity, resulting in ineffective clearance of A $\beta$  (Du et al., 2021). These findings suggest a potential association between FOXO3, A $\beta$  pathology and AD, as mitochondrial dysfunction and impaired cellular metabolism are critical features.

From a metabolic perspective, the hypothesis that FOXO3 might serve as a common pathway connecting AD and menopause shows promising. Studies have extensively explored the relationship between FOXO3, metabolic function, and cellular stress mechanisms (Cao et al., 2023; Omorou et al., 2023; Orea-Soufi et al., 2022). To look deeper into FOXO3's role in females, studies have demonstrated that increasing its expression enhances ovarian function in female mice, whereas its absence results in a decrease in functional ovarian follicles, potentially leading to premature aging, infertility and menopause (Castrillon et al., 2003; Hosaka et al., 2004). Since estradiol plays a vital role in regulating glucose metabolism, its decline contributes to metabolic disorders, characterized by reduced glucose metabolism, a condition observed in both AD (Mosconi et al., 2008) and menopause (Mosconi et al., 2021;

Mosconi et al., 2017a). When glucose levels are low, FOXO3, which is a target of AMP-activated protein kinase (AMPK) (Lee et al., 2020) becomes phosphorylated, triggering processes that regulate mitochondrial homeostasis (Herzig and Shaw, 2018). Acting as a cellular sensor for metabolic substrates, AMPK detects increased AMP and ADP levels (ATP/ADP-AMP ratio), indicating low energy availability due to decreased glucose. This activation promptly shifts towards catabolic processes, suppressing anabolic pathways. Ultimately, AMPK phosphorylates proteins involved in metabolic pathways, such as glycolysis (Wu et al., 2013; Marsin et al., 2000), to promote mitochondrial homeostasis (Toyama et al., 2016; Zong et al., 2002), and increase ATP levels.

A shared set of pathological features, including hypometabolism and A $\beta$  accumulation, characterizes both AD and menopause. Interestingly, A $\beta$  levels increase in the brains of females during menopause (Mosconi et al., 2021; Mosconi et al., 2017a; Mosconi et al., 2017b), suggesting a link between hormonal changes and progression of neurodegenerative diseases. To explore the connection between A $\beta$  with FOXO3, Shi et al. (2016a, 2016b) investigated the effects of A $\beta$  on HT22 mouse hippocampal neurons and primary neurons. They found that A $\beta$  induces FOXO3 dephosphorylation, leading to its relocation to mitochondria. Within the mitochondria, FOXO3 interacts with mitochondrial DNA (mtDNA) and disrupts oxidative phosphorylation by downregulating cytochrome oxidase subunit 1 (COX1) expression and COX activity (Shi et al., 2016a). Importantly, these mitochondrial impairments can be reversed by knocking down FOXO3, highlighting its pivotal role in cellular response stress.

Building on this, Fernandez et al. (2016) proposed that the calcineurin-FOXO3 pathway might exacerbate mitochondrial damage in astrocytes due to A $\beta$ . In particular, activation of this pathway triggers the release of pro-inflammatory cytokines, such as TNF- $\alpha$  and IL-6 in astrocytes (Fernandez et al., 2016), amplifying neuroinflammation and contributing to neurodegeneration. Additionally, CDK5 directly phosphorylates FOXO3 at specific residues (S325, 294, S173 and S24) in HT-22 cells, enhancing its nuclear translocation and levels (Shi et al., 2016b). While nuclear FOXO3 initially protects cells by upregulating MnSOD, a key antioxidant enzyme possibly mediated by ER $\beta$  and SIRT3 (Panza et al., 2017), prolonged activation shifts its role to promoting cell death by upregulating the pro-apoptotic Bim and FasL. This is crucial, as it seems that FOXO3 activation augments A $\beta$  levels and this is dependent on its phosphorylated status (Shi et al., 2016b). These effects can be mitigated by depleting CDK5 or FOXO3. Finally, in animal models of AD, nuclear FOXO3 localization occurs earlier, preceding neurodegeneration and A $\beta$  plaque formation (Shi et al., 2016b). These findings suggest FOXO3's dual role in regulating oxidative stress, mitochondrial function and neuroinflammation – key contributors to AD pathology-dependent on cell type and stress context.

FOXO3's role in insulin signalling further suggests a potential connection between menopause and AD. During the postprandial phase, pancreatic  $\beta$ -cells release insulin in response to elevated plasma glucose levels. Insulin binds to its receptors, initiating autophosphorylation on tyrosine residues and triggering the activation of PI3K. This sets off a downstream cascade that leads to AKT phosphorylation, critical step in insulin-mediated signalling. Activated AKT regulates glucose transporters like GLUT4, facilitating glucose uptake (Beg et al., 2017). Once phosphorylated, AKT translocates to the nucleus, where it phosphorylates FOXO3, driving its export from the nucleus. This process supports metabolic cycles essential for glucose utilization, including glycolysis and the Krebs cycle, while promoting glycogenesis and lipogenesis. In addition, phosphorylated AKT inhibits glycogen synthase kinase-3 beta (GSK-3 $\beta$ ), a protein implicated in apoptosis, tau phosphorylation, and A $\beta$  production (Gupta et al., 2022; Xing et al., 2018; Gonzalez-Reyes et al., 2016; Jaworski et al., 2011; Phiel et al., 2003). However, insulin resistance - commonly observed in postmenopausal females and AD patients (Sedzikowska and Szablewski, 2021; Kshirsagar et al., 2021; C et al., 2012; Catalano et al., 2008) - can disrupt this critical pathway. For

instance, reduced insulin levels or increased resistance may cause FOXO3 to remain in the nucleus, potentially driving the transcription of pro-apoptotic genes (Dijkers et al., 2002), hyperphosphorylated tau, and A $\beta$  accumulation. This dysfunction may stem from decreased p-AKT levels, which fail to sufficiently inhibit GSK-3 $\beta$ , exacerbating these pathological effects. Moreover, A $\beta$  itself might interfere with p-AKT-induced FOXO3 phosphorylation, further promoting FOXO3 nuclear retention. Elevated FOXO3 activity in the nucleus induces the expression of apoptotic proteins like BIM (Dijkers et al., 2002; Sanphui and Biswas, 2013), ultimately leading to neuronal apoptosis. Importantly, these processes are not limited to neurons. In astrocytes, the insulin/PI3K/AKT signalling pathway strongly affects FOXO3 subcellular localization, suggesting the presence of a conserved mechanism involving insulin, PI3K and FOXO3 that regulates metabolism and impacts lifespan (Du et al., 2021). Together, these mechanisms reveal how insulin resistance and A $\beta$  may synergistically contribute to AD pathology by disrupting FOXO3 regulation, emphasizing a potential link between metabolic dysregulations and disease progression.

## 7. Conclusions

Cognitive decline associated with menopause and AD represents a significant global health challenge, with far-reaching implications for patients' quality of life and healthcare systems. Despite extensive research efforts, effective treatments capable of fully halting or reversing AD progression remain unavailable. Current therapeutic approaches primarily aim to alleviate symptoms and delay disease progression, emphasizing the urgent need for deeper insights into the underlying pathology to identify novel therapeutic targets.

This review highlights the critical role of FOXO3 as a potential metabolic link between menopause and AD. FOXO3's involvement in cellular stress responses, metabolic regulation, and mitochondrial regulation positions it at the intersection of these conditions. However, its precise role is highly nuanced and context dependent. Evidence suggests that FOXO3 activity can have either protective or detrimental effects depending on factors such as cell type, tissue environment, and specific pathological insults. Additionally, FOXO3's regulatory influence on mitochondrial dynamics, oxidative stress, and glucose signalling highlights its importance as a shared molecular mediator. Elucidating these complex connections could yield valuable insights into the development of targeted therapies aimed at mitigating AD. Finally, a more comprehensive understanding of FOXO3's multifaceted roles may pave the way for designing precise, effective treatments tailored to address the unique vulnerabilities associated with menopause and AD.

## CRedit authorship contribution statement

**Christopher O'Mahony:** Writing – review & editing, Writing – original draft, Software, Investigation, Formal analysis, Data curation.  
**Oscar Hidalgo-Lanussa:** Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Investigation, Data curation.  
**George E. Barreto:** Writing – review & editing, Writing – original draft, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

## Ethics approval

N/A

## Consent for publication

All the authors consent for publication.

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## Declaration of competing interest

None.

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## Data availability

Data were retrieved from the databases used in this paper and is freely available.

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