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Review article

Sexual hormones regulate the redox status and mitochondrial function in the brain. Pathological implications

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ABSTRACT

Compared to other organs, the brain is especially exposed to oxidative stress. In general, brains from young females tend to present lower oxidative damage in comparison to their male counterparts. This has been attributed to higher antioxidant defenses and a better mitochondrial function in females, which has been linked to neuroprotection in this group. However, these differences usually disappear with aging, and the incidence of brain pathologies increases in aged females. Sexual hormones, which suffer a decrease with normal aging, have been proposed as the key factors involved in these gender differences. Here, we provide an overview of redox status and mitochondrial function regulation by sexual hormones and their influence in normal brain aging. Furthermore, we discuss how sexual hormones, as well as phytoestrogens, may play an important role in the development and progression of several brain pathologies, including neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, stroke or brain cancer.

1. Introduction

Oxidative damage and mitochondrial dysfunction play an important role in the development and progression of brain disease [1]. Women seem to be protected at young ages from the development of several brain pathologies, including neurodegenerative diseases, stroke, and cancer. Nevertheless, this protection disappears amongst post-menopausal women and the incidence and/or severity of these diseases significantly increase in this group, which suggests a protective role of estrogens regulating oxidative stress [2].

It is well known that H_2O_2 can act as a second messenger in the cell targeting several regulatory proteins, such as phosphatases, proteases or transcription factors [3,4]. However, excessive amounts of H_2O_2 and/or other ROS can become pathologic as they damage cellular structures if not neutralized properly [5,6]. For this reason, ROS production and scavenging are tightly regulated in the cell, through the activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and the glutathione peroxidase/reductase (Gpx/GRd) and peroxiredoxin/thioredoxin systems (Prx/Trx). Furthermore, mitochondrial function is also controlled by uncoupling proteins (UCPs), which dissipate the proton gradient generated by the respiratory chain and reduce ROS production [7,8], and some sirtuins (SIRTs), which deacetylate several proteins involved in redox regulation [9].

Most of the proteins implicated in the regulation of redox status and mitochondrial function are under the control of sexual hormones, which could be the reason why young women are more protected against brain injury [10]. Thus, mitochondrial function and antioxidant enzymes, and their differences with gender and aging, have been widely studied to better understand both normal function of the brain and their pathological implications. In this review, we first describe the regulation of antioxidant enzymes and mitochondrial function by sexual hormones. Second, we address the main changes that occur in the brain with aging, and finally, we discuss the influence of sexual hormones on several brain pathologies.

2. Sex hormones and redox regulation

Redox homeostasis and mitochondrial function show sex differences in the brain [11], as well as some pathologies or synaptic transmission related-mechanisms [12,13] that have been described as sex specific

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Abbreviations

2-ME2	2-methoxyestradiol
Aβ plaques	amyloid-β plaques
AD	Alzheimer's disease
AKT	protein kinase B
ALS	Amyotrophic lateral sclerosis
AMPK	AMP-activated protein kinase
AP-1	activator protein-1
AR	androgen receptor
BAT	brown adipose tissue
CAT	catalase
CREB	cyclic AMP response element binding protein
EGFR	epidermal growth factor receptor
eNOS	endothelial nitric oxide synthase
ERE	estrogen response elements
ERK	extracellular signal-regulated kinases
GABPα	GA-binding protein alpha
GPER	G protein-coupled estrogen receptor
GPx	glutathione peroxidase
GRd	glutathione reductase
GSH	reduced glutathione
GSSG	oxidized glutathione
HD	Huntington's disease
Htt	huntingtin
IDH2	isocitrate dehydrogenase 2
αKGDH	α-Ketoglutarate dehydrogenase
mtDNA	mitochondrial DNA
NF-κB	nuclear factor-κB
Ngb	globin neuroglobin
NRF2	nuclear factor erythroid 2-related factor
NRF-1/NRF-2	nuclear respiratory factors 1 and 2
OXPHOS complexes	oxidative phosphorylation complexes
PD	Parkinson's disease
PGC-1α	coactivator peroxisome proliferator-activated receptor gamma coactivator 1 α
PPARα	peroxisome proliferator-activated receptor alpha
Prx	peroxiredoxin
ROS	reactive oxygen species
SIRTs	sirtuins
StAR	steroidogenic acute regulatory protein
SOD	superoxide dismutase
TFAM	mitochondrial transcription factor A
Trx	thioredoxin
TrxR	thioredoxin reductase
TSPO	translocator protein
UCPs	uncoupling proteins
WAT	white adipose tissue

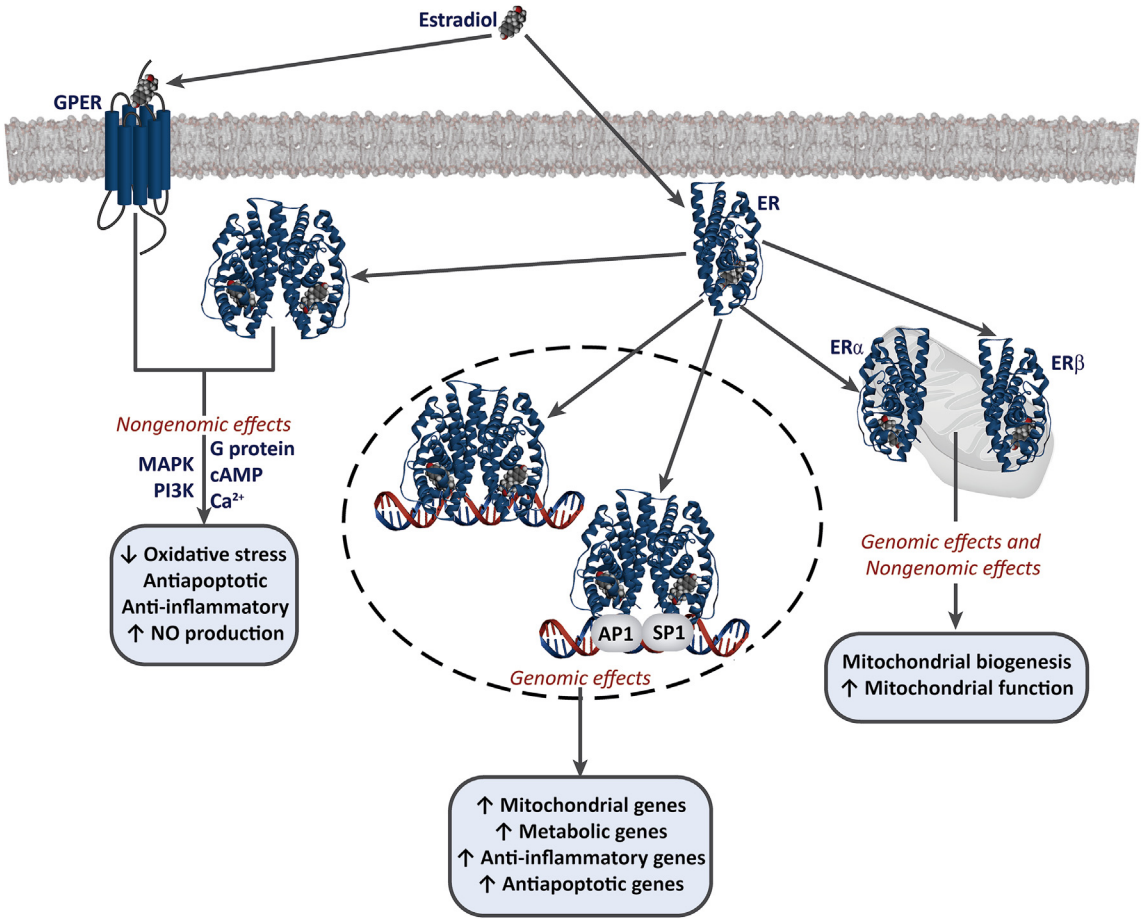

Fig. 1. Mechanisms involved in the regulation of redox homeostasis by estradiol. Estradiol can exert its effects by binding to the ERs (ERα or ERβ) or to GPER. Active ERs may bind to the promoter of target genes, which contain an ERE element. Genomic effects include the upregulation of several mitochondrial and metabolic genes, as well as anti-inflammatory and anti-apoptotic genes. Non-genomic effects, such as a reduction of oxidative stress, apoptosis avoidance or anti-inflammatory effects, are mediated through several protein kinases activated by these estrogen receptors.

processes [14]. Redox homeostasis in the brain is highly important, as an imbalance may contribute to the pathophysiology of many neurologic diseases [15,16].

Sex differences on oxidative stress in the brain, including free radical production, oxidative damage and antioxidant enzymes levels and/or activity, have been studied for a long time [14]. Some investigations show higher oxidative damage in lipids, proteins and DNA in male rats than in females [17–26]. This oxidative damage is due to a higher ROS production in male rats [20,22,27–29] and, moreover, lower antioxidant enzymes levels and/or activity [18,22,23,30–34]. It is worthy to note that, although these studies support a better redox homeostasis in female than in male rats, other reports show no differences [26,33,35–38]. Some authors suggest that age could be responsible for this controversy [31]. In fact, young brains of female rats show higher SOD [18,27,28,31,34] and CAT levels [18,30,32] than male rats of the same age, whereas in older rats these differences are not observed. Moreover, this controversy could be also explained if different parts of the brain are considered. For example, Noschang et al. reported that CAT levels were higher in the striatum of female brain rats, but male rats showed increased CAT levels in the prefrontal cortex. On the other hand, SOD levels were higher in the prefrontal cortex of female rats, and striatum SOD activity was similar in both sexes [34].

Sexual steroid hormones could be the reason of these sex differences observed in the regulation of redox homeostasis in the brain [39]. Sex hormones are steroids derived from cholesterol and are produced by the gonads, the adrenal glands and the placenta. They can reach and cross the blood-brain barrier and enter the central nervous system, where they modulate several physiological functions [40]. In addition, some neurons and glial cells are also capable of synthesize sex hormones *de novo* independently from peripheral tissues, which are commonly referred to as neurosteroids. These neurosteroids are chemically and biologically identical to circulating steroids [40,41]. Mitochondria are involved in steroidogenesis, as the first and rate-limiting step consists in the transfer of cholesterol inside these organelles. Acute regulatory protein (StAR) and translocator protein (TSPO) have been identified to participate in this transport [42]. Then, cholesterol is converted to pregnenolone, the precursor of steroids, by the cytochrome P450 side-chain cleavage enzyme. Finally, pregnenolone is transported outside the mitochondria and can be converted into the different sex hormones by specific enzymes [10]. Some studies suggest that the enzymes involved in neurosteroidogenesis show a sex-dependent pattern, contributing to the different levels of sexual hormones observed in males and females, although this has been proven in animal models and still needs to be addressed in humans [43].

Female sexual hormones, 17β-estradiol (E2) and progesterone, possess neuroprotective effects *in vivo* and *in vitro* at physiological concentrations [44–47]. However, male steroids, androgens and testosterone, usually present neurotoxicity [45,48]. Neuroprotective effects of sexual hormones can occur through genomic and non-genomic mechanisms [14]. Genomic mechanisms are triggered through the interaction with their receptor: the estrogen receptor (ER) α or β [49], the progesterone receptor [50] or the androgen receptor (AR) [51]. Interestingly, it seems that, at physiological concentrations, E2 is involved in neuroprotection through the activation of ERα and not ERβ, as seen by the reduction in the extent of cerebral injury in a mouse model of stroke, while at pharmacological concentrations, E2 activates ER-independent mechanisms [52]. In the classical pathway, the hormone binds to its receptor in the plasmatic membrane or in the nucleus, and this hormone-receptor complex binds directly to the promoter of target genes, through the estrogen response elements (ERE). There are alternative pathways in which the hormone-receptor complex interacts with other transcription factors that bind to DNA, such as activator protein-1 (AP-1) [53], cyclic AMP response element binding protein (CREB) [54], or nuclear factor-κB (NF-κB) [55], being this one especially important since it is known to activate key regulatory genes for maintaining the redox homeostasis of the cell.

Sexual hormones can also activate G-protein-coupled receptor pathways, protein kinases that lead to phosphorylation and activation of transcription factors, resulting in non-genomic effects. One example of this mechanism can be observed with the nuclear factor erythroid 2-related factor (NRF2) estrogenic activation by phosphatidylinositol 3-kinase and glycogen synthase kinase 3β pathways [56]. Finally, whichever the route of activation, the maintenance of redox homeostasis through sex hormones occurs due to the increase in the expression and/or activity of antioxidant enzymes such as SOD, CAT and GPx [14] (Fig. 1).

Moreover, estrogens may also modulate metabolic pathways through an increase of the expression of some electron transport chain proteins, such as cytochrome C and complex IV subunits, as well as citrate synthase enzymatic activity [57]. This control on the respiratory chain through sexual hormones is not only due to the ERE presence in the promoter of these genes, but also to the coordination of mtDNA transcription through nuclear transcription factors that are regulated by sexual hormones [39]. In fact, estrogens stimulate the transcription of nuclear respiratory factors 1 and 2 (NRF-1 and NRF-2), coactivator peroxisome proliferator-activated receptor gamma coactivator 1 α (PGC-1α) and mitochondrial transcription factor A (TFAM), which are involved in mtDNA transcription [58].

Estrogen-related receptor alpha (ERRα), an orphan nuclear receptor, also modulates estrogen signaling [59] and can be coactivated by PGC-1α. ERRα plays an essential role in the regulation of ROS generation [60], and mitochondrial function through the regulation of genes involved in mitogenesis and oxidative phosphorylation, and regulation of mitochondrial replication through TFAM activation [61]. Moreover, PGC-1α induces ERRα and, as PGC-1α mRNA levels increase, ERRα mRNA levels also increase [62].

Finally, phytoestrogens are a huge group of natural compounds which have been found in an extensive number of plants. The common characteristic of these compounds is that they present a chemical structure similar to estrogens and harbor some estrogenic activity [63]. For this reason, phytoestrogens could act through their interaction with the estrogen receptors, although they are able to exert their effects in an ER-independent manner. It is well known that phytoestrogens show antioxidant and anti-inflammatory activities [64], among others, and because of these properties, phytoestrogens could influence the normal function of the brain and modulate the molecular basis of the disease or, at least, palliate some of the symptoms. Phytoestrogens are also able to modulate the activity of ERRα through its direct interaction and activation as agonists [65]. Thus, phytoestrogens modulate mitochondrial biogenesis and function regulating the expression of NRF1, GABPα and PPARα through their interaction with ERRα [66].

3. Sex hormones and uncoupling proteins

UCPs are a family of proteins of the internal mitochondrial membrane whose function is to uncouple the electron transport chain form oxidative phosphorylation, dissipating the proton gradient, causing a decrease in membrane potential [67]. The reduction of the proton gradient contributes to decrease the production of ROS [68].

Five different isoforms of UCPs have been characterized. UCP1 was the first to be described in brown adipose tissue (BAT), tissue in which this protein enables thermogenesis particularly for newborns as well as hibernating animals [69]. UCP2 is expressed in most tissues, but especially in the immune system [67,70,71]. UCP2 has also been extensively investigated in the brain and has been found in different areas. Although there is not much evidence for the thermogenic role of UCP2 in the brain, some studies in rats have shown that it may create temperature variations that could affect the transmission of signals between neurons, increasing the traffic of neurotransmitters [72]. Moreover, it has been described that UCP2 is relevant for adaptive responses in cortical and hippocampal neurons, as well as for perinatal hypoxia-triggered circuit adaptations [73]. Whereas UCP3 is expressed

mainly in muscle and BAT [74,75], UCP4 and UCP5 (also known as brain mitochondrial carrier protein 1) are expressed mainly in the brain [67,76–78].

The role of UCP2, UCP4 and UCP5 in oxidative stress modulation of mitochondrial ROS is very clear [72,76,79]. UCP4 has a neuroprotective role in early neuronal development, while UCP5 and UCP2 are important for decreasing ROS production in neurons. All three UCPs have been found decreased in Alzheimer's disease patients, while both UCP4 and UCP5 have been described as protector factors for Parkinson's disease. This reduction of ROS promoted by UCPs in the nervous system could be relevant to avoid or ameliorate neurodegenerative diseases, including Alzheimer's and Parkinson's disease or lateral amyotrophic sclerosis [20,76,78].

Different studies have shown that UCPs are differentially expressed between males and females in animal models, although few of them focus on the brain. UCP1 levels are higher in female than male rats in BAT [81–84]. UCP2 levels are also higher in females in BAT [81] and in white adipose tissue (WAT) [82]. In skeletal muscle and WAT, females show increased levels of UCP3 when compared to males [82,85]. In the brain, UCP4 and UCP5 are higher in females [78]. Both proteins are also affected by age, as UCP4 decreases in older males, while no differences are observed in females, and UCP5 levels follows the opposite pattern, increasing with age in females while they are not affected in males [78].

These differences between males and females can be attributed to the effect of sexual hormones [86], as several studies carried out in primary mouse cultures or cancer cell lines have demonstrated that E2, progesterone and testosterone regulate the expression of these proteins [87–89]. In general, female hormones upregulate UCPs, while testosterone downregulates these proteins. Nevertheless, it should be noted that their action is dependent on the tissue and ratio ERα/ERβ. This way, as mentioned before, it seems that E2 exerts its neuroprotective effects through the activation of ERα [52], although some reports suggest that this protective effects, as well as the induction of UCPs, depends on the abundance of ERβ in the tissue [89–92]. This would be consistent with the fact that genistein, which shows higher affinity for ERβ, has a protective effect for mitochondria, enhancing their function and increasing the antioxidant response and expression of UCPs [92–94].

4. Sex hormones and sirtuins

SIRTs belong to a family of histone deacetylases that are dependent on NAD^+ for their enzymatic activity, which makes them cellular energy sensors. Some SIRTs also show other enzymatic activities, such as ADP-ribosylation or desuccinylation [95]. Up to seven isoforms (SIRT1-SIRT7) have been identified in mammals, and all of them are expressed in the brain, although they may suffer changes in their expression with aging [96].

The most studied sirtuins are SIRT1 and SIRT3. SIRT1 directly regulates mitochondrial biogenesis through deacetylation of PGC-1α [97], while SIRT3 is critical for reducing oxidative stress and maintaining proper mitochondrial function by regulating both expression and deacetylation levels of several antioxidant proteins [98,99]. It has been reported that SIRT1 levels in mice are modulated by age and sex, and this modulation is area specific in the brain [100]. In humans, SIRT1 also shows a sex-dependent pattern, as its enzymatic activity in serum was found to peak at different ages for men and women [101]. Furthermore, SIRT1 activity in serum and skin was significantly reduced with age, especially for women [101,102], suggesting a role of estrogens in the modulation of SIRTs.

Interestingly, sirtuins have also been described as potent modulators of sexual hormones receptors. SIRT1 has been identified as a coactivator of ERα, but not ERβ, through an independent mechanism not involving deacetylation [103–105]. However, other studies report SIRT1 as a negative regulator of ERα and AR through deacetylation [103] or by inducing AKT-dependent phosphorylation of the receptor [106].

Several reports confirm that sexual hormones regulate the levels of some SIRTs by several mechanisms. Upon activation, ERα is directly involved in the activation of transcription of the *SIRT1* gene [104,107–109], which has been associated to protection from cell stressors. For instance, in some rat models, E2 treatment activated SIRT1 in the brain, which resulted in the deacetylation of NF-κB [107] or p53 [110] and the inhibition of proinflammatory and proapoptotic proteins, significantly reducing oxidative stress. Furthermore, E2 induction of SIRT1 seems to be essential for the activation of AMPK and protection from ischemic brain injury [111]. Nevertheless, E2 was reported to reduce the expression of SIRT1 through the activation of Akt/ERK pathway in smooth muscle cells, suggesting that the effects of sexual hormones in SIRT regulation might be tissue dependent [112].

On the other hand, GPER has been also identified to be involved in the upregulation of SIRT1 through the activation of EGFR/ERK/c-fos/AP-1 pathway [113]. Furthermore, activation of AR by testosterone has also been described to regulate SIRT1 expression through the induction of eNOS, which prevented cellular senescence in mice [114].

Fewer studies have linked sexual hormones with SIRT3 modulation. ERβ has been found to recruit some transcription factors, such as Sp1, in the promoter of the *SIRT3* gene [115]. ERα might also be involved in the expression of SIRT3, as this receptor induces the expression of Nrf-2, which stimulates an antioxidant response involving also SIRT3 [116]. Notably, it has also been reported that PGC-1α and ERRα can upregulate SIRT3 expression and protein levels [117].

Moreover, 2-methoxyestradiol (2-ME2), a naturally occurring metabolite of E2, regulates both SIRT1 and SIRT3 levels. 2-ME2 has been reported to upregulate SIRT1 protein levels to trigger autophagy [118], while it inhibited SIRT3 activity through physical interaction, resulting in a decrease of mitochondrial mass and activity [119]. Finally, some phytoestrogens have shown the potential to modulate both SIRT1 and SIRT3, presumably through the activation of ER, such as genistein [120], hop-derived phytoestrogens [121] and resveratrol [122].

5. Sex hormones and aging

Brain aging is linked to a decline in mental functions, as well as the development of neuronal dysfunction. This deterioration has been related to a decrease in the levels of sexual hormones with age. Therefore, it has been postulated that the reduction in sex hormone levels could aggravate neuronal dysfunction associated with age [39].

In general, a decline in mitochondrial function and antioxidant capacity in the brain has been described with normal aging [39]. Due to the high metabolic rate and increased sensitivity to oxidative stress, the brain is especially dependent on proper mitochondrial function and an ideal oxidative balance [123]. For this reason, and the relative low levels of antioxidant defense systems, the brain is especially susceptible to oxidative damage [123,124]. Upon oxidative stress in the brain, NRF2 becomes activated to increase the expression of several antioxidant enzymes, and other small antioxidant molecules participate in detoxification of radical species. However, it seems that neurons from some regions of the brain, such as hippocampus, amygdala and prefrontal cortex, are more susceptible to oxidative damage [125].

Among other evidence, a decrease in the activity of α-ketoglutarate dehydrogenase (αKGDH), enzyme of the TCA cycle, has been described during aging. This reduction is related to higher oxidative stress [126] and to an increase in peroxidation of cardiolipin. This lipid, present in the internal mitochondrial membrane, is associated with the inhibition of the complex IV and the worsening of the respiratory chain function in the brain [127–129]. It is necessary to emphasize that there are differences among the different areas of the brain. In this sense, mitochondria of the hippocampus of rats appear to be more susceptible to the effect of age than other areas [130]. Although there are fewer studies in humans, some authors describe a decrease in the activity and

protein levels of complex IV in different cerebral sub-regions [131,132], and, more recently, an increase in oxidative damage in mitochondria in the frontal and hippocampus cuts [133]. On the other hand, a deterioration in the capacity of learning and memory, as well as a decrease in the neurogenesis of the hippocampus, have been described with age, and this process could be also modulated by oxidative stress [134].

The brain also suffers a decrease in sexual hormone levels with age, as a result of the decrease in the peripheral synthesis and neurosteroidogenesis, and a more drastic pattern is exhibited in women than in men due to menopause [135]. A decrease in levels of E2, progesterone, testosterone and related metabolites has been described in 24-month-old male mice compared to 7-month-old mice [136], and an age-induced decrease in progesterone levels in mice has also been reported [137]. As mentioned before, mitochondria play an important role in steroid synthesis, so any alterations in mitochondrial function can also affect the levels of sex hormones.

In this regard, previous studies in our laboratory concluded that aged female rat brains had more differentiated mitochondria with greater functional capacity than male brains, and showed a better control of oxidative stress balance, which could be due, in part, to the neuroprotective effect of UCPs [138,139]. The ratio mitochondrial protein/DNA content decreased with aging, shifting towards worse mitochondrial functional capacity and increased mitochondria number [139]. The effect of aging was less marked in females, which accumulated less oxidative damage than males due in part to their greater antioxidant capacity, such as higher GPx activity and higher UCP5 levels. Furthermore, these sex differences gradually increased during aging [140].

In accordance with these studies, other authors have reported that women possess higher antioxidant defenses than men [141,142]. Moreover, in female ovariectomized rats, oxidative stress levels were comparable to those exhibited by males, and a treatment with E2 reverted the effect of the ovariectomy [27,141]. The drop in sex hormones has also been related to a shift to a ketogenic metabolism, with a marked reduction in COX activity and ATP production, and higher oxidative stress [143,144].

Epidemiological data suggest that sex hormones are also involved in the development of several brain pathologies, which will be further developed in the next section of this review. For instance, ischemic strokes occur more frequently among elderly people, and women have a higher risk of suffering this disease and, more concerningly, a poorer functional recovery than men. This trend is repeated in experimental animals, as older females show a more extensive loss of brain tissue than adult females [145].

6. Sex and phytoestrogens influence in the development of brain pathologies

Brain pathologies, especially neurodegenerative disorders, suppose a growing burden as population ages and show a sexual dimorphism in both their incidence and severity. As has been mentioned throughout this review, women seem to be protected at young ages from the development several brain diseases, although the incidence of these pathologies increases after menopause [2]. Moreover, phytoestrogen consumption has been thought to be a key modulator in oxidative stress in the brain and, therefore, to have important effects over brain pathologies development and progression. Twenty years ago, Gélinas and Martinoli demonstrated the protective effects of phytoestrogens on oxidative stress in rat neuronal cells PC12 [146]. More recently published *in vivo* studies have shown the positive effects of phytoestrogens on cognitive function and the improvement of mitochondrial functionality after phytoestrogen consumption in ovariectomized rats, decreasing the oxidative damage in these animals [147,148]. Moreover, there are clinical trials that relate the consumption of these compounds with a decrease in oxidative stress [149,150] and with a better cognitive ability and a decrease in the risk of suffering from

Table 1
Most studied phytoestrogens, main sources and effects on different brain pathologies.

Phytoestrogen	Main Sources	Disease	Effects	References
Genistein	Soy	Alzheimer disease	Reduces oxidative stress induced by β-amiloid accumulation and activates p38	[166]
		Amyotrophic lateral sclerosis	Inhibits the tyrosine kinase activity, avoiding the action of ROS mediators	[196]
		Huntington's disease	Improves the disease symptoms and the inflammatory and oxidative profile and inhibits the cholinesterase activity	[204]
		Stroke	Reduces the cell death of primary cortical neurons subjected to ischemic-like injury *in vitro*	[213]
Daidzein	Soy and red clover	Alzheimer disease	Improves the cognitive dysfunction and reduces oxidative stress	[167]
		Parkinson's disease	Decreases the inflammation	[182]
		Stroke	Reduces the cell death of primary cortical neurons subjected to ischemic-like injury *in vitro*	[213]
		Brain cancer	Protective role against gliomagenesis	[217]
Resveratrol	Grapes, mulberries and peanuts	Alzheimer disease	Induces the expression of sirtuin 1 improving the mitochondrial function and reducing the oxidative stress	[168,169]
Quercetin	Apples, onions and tomatoes	Alzheimer disease	Restores the cognitive functions reducing the release of β-amiloid	[170]
		Parkinson's disease	Reduces the expression of proinflammatory cytokines and superoxide anion production, provoking a decrease in the apoptosis ratio of neuronal cells	[187–189]
Coumestrol	Soy, alfalfa and clovers	Parkinson's disease	Decreases the inflammation	[182]
Formononetin	Legumes	Parkinson's disease	Inhibits neuroinflammation and increases ERβ protein expression improving mitochondrial function	[183]
		Brain cancer	Restores mitochondrial function and inhibits cell signaling and invasion pathways	[233]
Epigallocatechin-3 gallate	Green tea and chocolate	Parkinson's disease	Reduces ROS production	[185]
Biochanin A	Lentils, red clover, alfalfa and cabbage	Stroke	Increases the expression of the glutamate oxaloacetate transaminase, which metabolizes the neurotoxic glutamate in the stroke-affected brain	[212]
		Brain cancer	Restores mitochondrial function and inhibits cell signaling and invasion pathways	[218]

neurodegenerative diseases such as Alzheimer's disease or dementia [151–153]. Table 1 summarizes the effects of the main phytoestrogens on different brain pathologies.

6.1. Alzheimer's disease

Alzheimer's disease (AD) is the major neurodegenerative disease amongst the elderly population [154]. AD is characterized by a progressive cognitive loss, significantly affecting short-term memory, speech and reasoning [155]. This is the result of a mitochondrial dysfunction caused by the accumulation of amyloid-β (Aβ) plaques and intracellular fibrillary tangles formed by an abnormal phosphorylation of tau protein [156]. Epidemiological studies suggest a strong correlation between sex and the incidence of AD, since about two thirds of AD patients are women [157]. Furthermore, women manifest a faster cognitive decline and evolution of AD than men, probably due to an increased Aβ accumulation [157,158]. Thus, the drop in estrogens after menopause is recognized as a risk factor for developing AD, since this reduction is associated to lower mitochondrial function and higher oxidative stress [159], as explained before. Some studies also point out that the decrease in androgens could also be related to an increase in AD incidence in men as they age [159–161].

These observations have been also reported in animal models, and some authors suggest that the administration of estradiol may be a strategy to reduce AD incidence [29,162,163]. Noteworthy, SIRT1 and SIRT2 have been found elevated in lymphocytes from AD patients, as well as a reduction in UCP1 [164]. Furthermore, phytoestrogens have been shown to also improve cognitive function in animal and human studies, and they can offer protection against the development of AD. The relationship between the phytoestrogens present in soybeans, such as daidzein and especially genistein, and the improvement of memory and cognitive capabilities has been demonstrated in studies from 20 years ago [153,165]. A recent paper determined that pre-treatment with 0.5 μM of genistein is able to reduce hydrogen peroxide production in neurons treated with β-amiloid, which could suggest that this phytoestrogen would have a protector effect against oxidative stress induced by the β-amiloid accumulation [166]. This protective effects of genistein could be due to the ability of this phytoestrogen to activate p38, a protein involved in the β-amiloid cytotoxicity [166]. Likewise, daidzein also improves the cognitive dysfunction and reduces the oxidative stress in streptozotocin AD-induced rats, restoring antioxidant enzymes and glutathione levels and reducing oxidative damage [167]. Other phytoestrogens like resveratrol are able to induce the expression of sirtuin 1 [168], improving the mitochondrial function and, ultimately, reducing the oxidative stress in cells [169]. Moreover, quercetin has also positive effects restoring the cognitive functions, also reducing the release of β-amiloid in Alzheimer-model transgenic mice [170].

6.2. Parkinson's disease

Parkinson's disease (PD) is characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra, and the presence of Lewy bodies. This results in the consequent depletion of dopamine [171] and the development of motor symptoms that include tremor, bradykinesia and rigidity, and other non-motor manifestations such as cognitive decline [172]. One of the possible causes of the appearance of this disease is neuroinflammation, a process characterized by the activated microglia and the up-regulation of proinflammatory gene expression [173]. In the case of PD, men present two-fold higher incidence rates than women, which has been observed in human patients and animal models [172,174,175]. Furthermore, women tend to develop PD at a later age than men, with milder symptoms and slower disease progression [176,177]. In addition, a more marked mitochondrial dysfunction has been described in men with PD with respect to women [178], suggesting a neuroprotective role for sex hormones. In fact, testosterone and estradiol levels were found reduced in male PD patients compared to healthy individuals, and higher levels of these hormones could be associated to better cognitive ability in PD patients [179]. Interestingly, UCP4 and UCP2 have been associated to a better mitochondrial function and protection from some motor symptoms of PD in mice [180,181].

A study carried out by Jantaratnotai and collaborators in 2013 demonstrated that soy phytoestrogens, like genistein, daidzein and coumestrol, were able to decrease both the expression of genes related to the inflammation and the activation of signaling pathways associated to the inflammatory process [182], which could delay PD progression. Formononetin, a non-steroidal isoflavone, inhibits neuroinflammation and increases ERβ protein expression in BV2 mouse microglia cells [183]. In addition to neuroinflammation, a prolonged situation of oxidative stress may stimulate the development and progression of PD [184]. Catechins are a group of polyphenols which can be found in vegetal products like tea and chocolate. Among them, epigallocatechin-3 gallate stands out, since it has the potential to reduce ROS production, increasing antioxidant enzymes expression [185]. Quercetin has also shown anti-inflammatory and antioxidant effects [186]. This phytoestrogen is able to reduce the expression of proinflammatory cytokines and superoxide anion production in microglial N9 cells [187], suggesting that quercetin could modulate the expression and activity of the electron transport chain complexes, provoking a decrease in the apoptosis ratio of neuronal cells [188,189].

6.3. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that affects motor neurons of the cortex, brain stem and spinal cord, resulting in neuromuscular dysfunction and paralysis [190]. The causes of sporadic ALS are still unknown, but it is believed that a mix between environmental and genetic factors may be responsible. A redox disbalance seems to be involved in the pathogeny, since a reduction in SOD1 or TrxR1 activities is found in most patients with ALS [191,192]. This disease is more frequent in men than women, although the difference is lost at older ages, and men usually show different clinical manifestations than women [193].

In a mice model for ALS, females also show a slower progression of this disease, although ovariectomy abrogates this difference and E2 treatment reverses its effects [194]. Furthermore, a better mitochondrial function and lower oxidative stress were reported in female mice [195], which are related to the presence of E2. Finally, some phytoestrogens such as genistein are able to act like a neuroprotector agent against this disease, mainly for its estrogenic activity and also for its ability to inhibit the tyrosine kinase activity, avoiding the action of ROS mediators [196].

6.4. Huntington's disease

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by an expansion mutation in the huntingtin (Htt) gene. HD patients suffer a wide range of motor, cognitive and psychiatric symptoms [197]. In the case of HD, women show a poorer prognostic, since they usually present a faster progression and more severe symptoms than men [198,199]. Interestingly, E2 treatment, through the activation of ERα, induces the expression of Htt in a dose- and time-dependent manner [200], as well as globin neuroglobin (Ngb) expression [201]. The interaction between Htt and Ngb confers neurons protection from oxidative stress and apoptosis. However, in striatal neurons with mutated Htt, the effect of E2 is abolished, and Htt and Ngb interaction is lost, resulting in increased apoptosis [202]. Furthermore, some SIRTs, especially SIRT1, seem to have a role in the development of this disease, as their expression is increased in some areas of the brain of HD patients and are associated to metabolic changes [203].

On the other hand, genistein can revert the effects of the 3-Nitropropionic acid, which is a mitochondrial toxin able to mimic the symptoms of HD in rodents [204]. In this study, carried out by Menze and collaborators in 2015, several effects of genistein have been checked in ovariectomized rats, reverting the main symptoms of the disease, such as the locomotive improvement and the increased retention latencies in the passive avoidance task. Genistein treatment improved the inflammatory and oxidative profile of the animals and, moreover, inhibited the cholinesterase activity [204].

6.5. Stroke

Stroke is caused by a reduction in the cerebral blood flow, which results in cell death due to the lack of oxygen and nutrients. Stroke is the leading cause of death in developed countries, and the incidence is higher in men than women, although this difference is lost in postmenopausal women. In fact, in the 10 years following menopause, the risk of stroke doubles in women and the outcome tends to be poorer [205,206]. E2 has been reported to have a neuroprotective role in some animals, including humans, by improving learning, memory, secondary symptoms such as depression, and by reducing the recovery time after a stroke [207–209]. Some genetic variants of UCP and SIRT genes have been associated to the development of stroke [210]. Interestingly, Guo et al. [111] recently showed that E2 treatment stimulates both expression and activity of SIRT1, which stimulates AMPK activation and results in neuroprotection from stroke. Furthermore, the activation of ERs may improve the severity and the outcome in females after stroke [211].

In the pathophysiologic setting of cerebral ischemia, excitotoxic levels of glutamate contribute to neuronal cell death. The isoflavone biochanin A has the capacity to increase the expression of the glutamate oxaloacetate transaminase, which metabolizes the neurotoxic glutamate in the stroke-affected brain [212]. In 2010, Schreihofer and Redmond discovered that daidzein, its metabolite equol, and genistein, were able to reduce the cell death of primary cortical neurons subjected to ischemic-like injury *in vitro*, exerting this effect in an ER-dependent manner, more concretely the ER-kinase pathway [213].

6.6. Brain cancer

Brain cancer is a relatively rare disease compared to other cancer types, although it is the second more common cancer in children. Approximately 23700 new cases per year are reported, accounting for the 1.4% of all new cancer cases [214]. Epidemiologic studies support a sex difference for brain cancer incidence, as men are twice as likely to develop medulloblastoma, ependymoma, and gliomas [215]. Furthermore, a recent study reported a better outcome and survival for women than men, as they responded better to the standard therapy, and identified specific transcriptome signatures for glioblastomas [216].

Oxidative stress and inflammation are involved in brain cancer development and progression, and since phytoestrogens have antioxidant and anti-inflammatory activities, they could be potential candidates for brain cancer prevention. An epidemiologic study carried out in San Francisco Bay Area in 2006 demonstrated that the consumption of foods containing phytoestrogens, especially daidzein, seems to have a protective role against gliomagenesis [217]. Moreover, recent studies showed that the combination of the phytoestrogens formononetin or biochanin A and the cytotoxic treatment temozolomide enhanced the anticancer effect in glioblastoma multiforme cells, with greater inhibition of cell signaling and invasion pathways, and restoring the mitochondrial function [218,219].

6.7. Other brain diseases

Other brain diseases such as autism spectrum disorders [220], depression [221], multiple sclerosis [222], or traumatic brain injury [223,224], also show gender differences in incidence and/or outcome, suggesting the influence of sex hormones. Some phytoestrogens, especially isoflavones like genistein or daidzein, have been used for the treatment of psychiatric disorders, taking advantage of their estrogenic activity [225]. For instance, the consumption of soy phytoestrogens can affect the immune system activation through an ERα-dependent pathway [226], which could modulate seizure propensity in epileptic patients [227]. An isoflavone-rich diet, with high amounts of genistein, daidzein and equol, can reduce the anxious behavior in mice [228]. Moreover, an epidemiologic study revealed that a soy-supplemented diet decreased the depression and anxiety levels in postmenopausal women [229]. In the same way, it has been proved that genistein administration decreased the dopaminergic activity in schizophrenic rat models [230]. Despite the numerous described beneficial effects of phytoestrogens, especially related to their antioxidant and anti-inflammatory properties, there are studies which link phytoestrogen consumption in the childhood with the increment of autistic behaviors [231]. In addition, large doses of genistein administered chronically may induce cytotoxicity and apoptosis in the rat brain [232]. This highlights the need to further study both sexual hormones and phytoestrogens and understand the molecular mechanisms involved in their effects.

7. Concluding remarks

Sexual hormones play a crucial role in the brain regulating mitochondrial function and the antioxidant response. This way, sexual hormones have a strong influence on oxidative stress, as they can modulate key proteins involved in these processes, such as antioxidant enzymes, UCPs and SIRTs. Even though sexual hormones could explain, at least in part, the sexual dimorphism observed for some brain pathologies, and studies in animal models support the idea of E2 as a potential treatment, the data from clinical trials involving patients remains questionable. Differences between both sexes need to be addressed both in preclinical and clinical studies, as well as age-related changes, to elucidate whether E2 supplementation could be a potential treatment, and to establish dose, time and form of administration. Nevertheless, a deeper understanding of the effects of sexual hormones in different brain pathologies could yield potential gender- and age-specific therapeutic interventions. Furthermore, molecules mimicking the effect of sexual hormones, such as phytoestrogens, could hold promise as new neuroprotective strategies, as they could stimulate antioxidant defenses and improve mitochondrial function, reducing oxidative damage and its influence in the development of brain pathologies.

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