Book Chapter

Mitochondria, Estrogen and Female Brain Aging

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Abstract

Mitochondria play an essential role in the generation of steroid hormones including the female sex hormones. These hormones are, in turn, able to modulate mitochondrial activities. Mitochondria possess crucial roles in cell maintenance, survival and well-being, because they are the main source of energy as well as of reactive oxygen species (ROS) within the cell. The impairment of these important organelles is one of the central features of aging. In women's health, estrogen plays an important role during adulthood not only in the estrous cycle, but also in the brain via neuroprotective, neurotrophic and antioxidant modes of action. The hypoestrogenic state in the peri- as well as in the prolonged postmenopause might increase the vulnerability of elderly women to brain degeneration and age-related pathologies. However, the underlying mechanisms that affect these processes are not well elucidated. Understanding the relationship between estrogen and mitochondria might therefore provide better insights into the female aging process.

Thus, in this review, we firstly describe mitochondrial dysfunction in the aging brain. Secondly, we discuss the estrogen-dependent actions on the mitochondrial activity, including recent evidence of the estrogen – brain-derived neurotrophic factor and estrogen – sirtuin 3 pathways, as well as their potential implications during female aging.

Keywords

Neurodegeneration; Female Brain Aging; Mitochondria; Estrogen; Protection; Bioenergetics; SIRT3; BDNF; E2

Introduction

Mitochondria play crucial roles in different aspects of cellular physiology, including calcium homeostasis, metabolism, apoptosis and ATP production [1]. At the electron transport

chain (ETC), especially at the respiratory complexes I and III, mitochondria produce reactive oxygen species (ROS) [2]. Mitochondrial respiration via ETC generates a flux of electrons that is coupled to a gradient of protons. During the oxidative phosphorylation (OXPHOS), electrons are neutralized to water upon reaction with oxygen at complex IV (cytochrome *c* oxidase), while the gradient of protons is necessary for the ATP synthesis via complex V (ATP synthase) [3].

Mitochondria are also essential sites for steroid hormone biosynthesis including estrogen, the main female steroid hormone [4]. Estrogen is involved in many physiological functions such as modulation of the effects of the trophic factors in the brain, enhancement of the cerebral blood flow, and prevention of atrophy of cholinergic neurons [5]. The estrogen family (E2) includes the hormones estrone, estradiol (17β-estradiol) and estriol, all of them playing a role in the estrous cycle. Regarding to the estrogenic effect, estradiol is the predominant form of estrogen and ten times as potent as estrone and about 80 times as potent as estriol. During reproductive senescence, a hormonal deficit occurs in menopausal women, characterized by a sudden decline in circulating estrogen level (Figure 1) [4]. Menopause officially marks the end of female reproduction. Postmenopause represents the years after the menopause while the transitional stage leading from reproductive years to permanent infertility that occurs immediately before menopause is termed perimenopause [6]. Perimenopause or "menopause transition" can begin 8 to 10 years before menopause, when the ovaries gradually produce less estrogen. It usually starts in the fourth decade of woman's life. In the last 1-2 years of perimenopause, the drop in estrogen accelerates (Figure 1) [6]. As a result of a lower level of estrogen, postmenopausal women seem to be at higher risk for a number of diseases, such as osteoporosis, heart disease and dementia [6].

In males, estradiol is known to be an active metabolic product of testosterone. The serum levels of estradiol in males are about 14-55 pg/ml and are comparable to those of postmenauposal women <35 pg/ml. Testosterone freely enters the brain and might be

converted to estradiol by local aromatase enzymes before acting at the cellular level [7]. In the central nervous system (CNS) of men and women, specific estrogen receptors have been shown to localize in mitochondria in the frontal lobe and the hippocampus, confirming an implication of estrogen in controlling memory processes and cognitive functions via energy supply [8]. Further studies have shown that estrogen plays an important neuroprotective role during the aging process, in particular through their beneficial impact upon mitochondrial metabolism [9]. Moreover, females live longer than males. This sex difference in life longevity can be attributed in part to the antioxidant effect of estrogen and the up-regulation of life longevity–related genes [10].

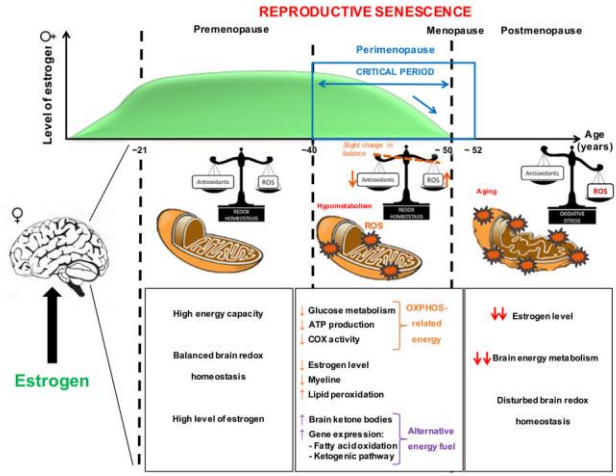

Figure 1: Potential sequence of pathological events occurring at the mitochondrial level during aging and «the critical time period» of decline in estrogen (E2) in female brain.

During the premenopause, high levels of estrogen are paralleled by a normal mitochondrial activity with a balanced redox homeostasis and a high brain energy metabolism. At the beginning of the reproductive senescence, or perimenopause, a decrease of estrogen levels is accompanied with an increase of oxidative stress (ROS levels) and, consequently, hypometabolism. During aging, alterations of the mitochondrial membrane lipid profile are also reported. Cells possess compensatory mechanisms, as antioxidant defenses, to keep the system in balance. In case the compensatory system is exhausted, metabolic impairments may occur, such as a decrease of ATP levels, glucose hypometabolism, and mitochondrial respiration (e.g., cytochrome c oxidase

(COX) activity) as well as myelin impairments. In parallel, an increased expression of genes involved in fatty acid oxidation and the ketogenic pathway were reported as an alternative fuel for cells. The “critical period” (represented by the blue arrow) indicates a fast drop of estrogen levels in a relatively short time period, suggesting a period of women’s life where they are more vulnerable and more likely to develop age-related brain disorders such as Alzheimer’s disease. Estrogen replacement therapies (ERT) may be beneficial before women reach a critical threshold of cellular damage during perimenopause and early after menopause. ROS: reactive oxygen species.

Normal cellular function can be disrupted by mitochondrial impairment which represents a key feature of the aging process [11,12]. The brain is our most energy-consuming organ and the age-dependent dysregulation in cerebral redox homeostasis and bioenergetics might therefore be able to trigger the development of neurodegenerative disorders.

Mitochondrial Impairments in Brain Aging: Insight into the Role of Estrogen

Aging is characterized by a progressive decline in physiological functions, often accompanied by neurodegenerative diseases and mitochondrial dysfunction is one of the main factors contributing to the aging process (Figure 2) [13].

During aging, energy production in the brain is reduced and, in parallel, the redox status is switched from an antioxidant to pro-oxidant state, partly due to the mitochondrial production of $O_{2}^{\cdot-}$ and H_2O_2 [14]. Globally, a reduction in mitochondrial functions, including the activity of ETC complexes as well as the antioxidant defense enzymes such as glutathione (GSH) and superoxide dismutase (SOD), was observed with increasing age (Figure 2) [15,16].

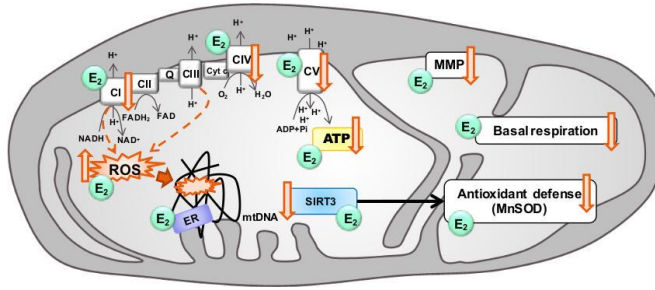

Figure 2: Modulation of mitochondrial function in aging by estrogen. Aging is associated with electron transport chain (ETC) impairments leading to decreased ATP levels, basal respiration, and mitochondrial membrane potential (MMP), together with a decrease of antioxidant defenses, and an increase of reactive oxygen species (ROS) production by complex I and complex III (dashed arrows) as well as mitochondrial DNA (mtDNA) oxidative damages. Estrogen (E2) has been shown, to increase ETC activity, stabilize the MMP, prevent the ROS production, and ameliorate the basal respiration and the production of ATP levels. Sirtuin 3 (SIRT3) and estrogen may converge on a common pathway to rescue mitochondrial activity in aging by increasing antioxidant defense activity. Estrogen and SIRT3 are suggested to rescue age-related impairments. ↓: age-related decrease, ↑: age-related increase.

We recently reviewed the age-dependent modifications in redox homeostasis and brain bioenergetics, both hallmarks of normal brain aging, with a specific focus on sex differences [17]. We highlighted the tight relationship between the age-related decrease in sex steroid levels and the age-related increase in brain oxidative insults. Especially, women experience a drastic loss of estrogen at the menopause that may be correlated with a decrease of antioxidant defenses (GSH levels) and increased oxidation in the brain (Figure 1) [17-19]. Strikingly, women are more armed against oxidative stress before the menopause due to their elevated antioxidant defense mechanisms compared to men [20]. Healthy young females (±26 years old) showed higher GSH levels in the frontal and parietal cortex compared to young men [19], with a progressive decrease during aging from young to old women (±56 years old). One of the relevant sources of ROS, the monoamine oxidase A (MAO-A) was found to be higher in the brain of perimenopausal women (41-51 years old) compared to young women (21-40 years old) [18]. In perimenopausal women who underwent bilateral oophorectomy, the serum estrogen levels were decreased and an increase of oxidative stress was

observed. This effect was prevented by a treatment with estrogen [21].

These human data are supported by numerous animal studies (reviewed in [9,17]. Namely, Yao and colleagues showed that in the brain of perimenopausal mice during reproductive senescence, the drop of estrogen and progesterone (the second female sex hormone) concentrations was accompanied by an increased expression of genes implicated in fatty acid oxidation and the ketogenic pathway, especially at an age between 9 and 12 months (Figure 1) [22]. Further investigations revealed that, in response to a glucose deprivation, the fatty acid metabolism was activated in the perimenopausal mouse brain. This increase was coupled with myelin degeneration as well as a rise of brain ketone bodies that were used as an alternative energy fuel (Figure 1) [22,23]. Thus, these findings highlighted the role of estrogen on the brain redox balance and energy metabolism at the menopause (Figure 1).

A growing body of evidence supports the mitochondrial theory of aging. The decreased functionality of complex I is often cited as the most likely site of an ETC impairment (Figure 2) [24-26]. Indeed, complex I activity is decreased across the brain in aged mice [27], together with a decrease of cytochrome *c* oxidase (COX, complex IV) activity and an increase of ROS production (Figure 2) (reviewed in [28]). Finally, modifications in the fatty acid profile of mitochondrial membranes that are more prone to peroxidation are induced by ovariectomy (OVX), and is a feature also reported in aging [29].

Mitochondrial DNA (mtDNA) is close to ROS produced by complex I and complex III and seems to be more susceptible to oxidative damage than nuclear DNA (nDNA) [30,31]. During normal aging, increased levels of oxidative modifications are reported in the brain as well as mutations in mtDNA [32,33]. Of note, no difference in mtDNA oxidative stress markers was detected between 10 months old male and female mice in the liver or the muscle [34]. However, since mtDNA is exclusively maternally inherited, female mitochondria appear to be better equipped to prevent mtDNA damage and mutation to reduce the

risk of producing inheritable metabolic disorders (reviewed in [35]). In line, estrogen supplementation was able to improve the transcription levels of several DNA repair enzymes involved notably in base excision repair pathway in the dorsal raphe of OVX old female macaques [36].

Mitochondrial dynamics play an important role in maintaining a healthy organelle population [28,37]. Impairments in this quality control system lead to the accumulation of defective mitochondria, as well as inefficient mitochondrial transport and distribution. Strikingly, only few studies were focused on mitochondrial fusion/fission activity in the brain during aging (see [28]. Alterations in the expression of fusion/fission proteins were shown in mice synaptosomal mitochondria, with namely an increase in dynamin-related protein 1 (Drp1) expression, a fission protein, between 5 and 12 months of age, and a decrease from 12 to 24 months [38]. In parallel, the expression of mitochondrial fusion proteins, including mitofusins 1/2 (Mfn1/2) and optic atrophy 1 (Opa1), decreased from 5 to 12 months and increased from 12 to 24 months, suggesting that synaptosomal mitochondria were shifted to a pro-fusion state in aged animals. Additionally, a pro-fusion effect of estrogen (increased mRNA and protein level of Mfn1/2) was shown in MCF-7 breast cancer cell line [39]. However, to our current knowledge, estrogen effects on mitochondrial dynamics in the brain remain still under investigated. An age-related decline in mitophagy (elimination of damaged mitochondria by autophagy) and mitochondrial biogenesis have also been previously reported (reviewed in [28]), but the precise reason for this decrease remains elusive, especially in the brain. It has been suggested that one of the potential mechanisms regulating mitochondrial biogenesis occurs via hormonal control such as estrogen (reviewed in [40,41]).

Thus, mitochondrial dysfunction seems to play a central role in brain aging, leading to decreased bioenergetics (glucose metabolism, mitochondrial respiration and ATP synthesis) and increased oxidation (increase of ROS and decrease of antioxidant defenses). High levels of estrogen, especially that of estradiol, before the menopause may be involved in the high energy

capacity as well as the control of redox balance in female brain (Figure 1). Then, the drastic drop of estrogen levels may disturb this finely controlled homeostasis, leading to the above mentioned impairments (see also [17]. The Figure 2 summarizes where estrogen can potentially act to prevent or rescue age-related mitochondria impairments (reviewed in [9,17], see also section: *ESTROGEN AND BIOENERGETICS IN FEMALE BRAIN: IMPLICATIONS FOR ESTROGEN REPLACEMENT THERAPY*).

Estrogen in the Central Nervous System

Mitochondria, Steroid Synthesis and Estrogen

Steroid hormones can be synthesized within the nervous system independently of peripheral steroid glands and are called neurosteroids [42]. Mitochondria play a crucial role during the first step of the steroid hormone biosynthesis which is the production of pregnenolone, the common precursor of steroids and neurosteroids [3]. The limiting step during steroidogenesis is the transport of cholesterol from the outside to the inside of mitochondria [43]. This process highlights the paramount role of mitochondria in steroid homeostasis. The interaction between the steroidogenic acute regulatory protein (StAR) and a multi-component molecular complex including an 18 kDa translocator protein (TSPO) regulates the cholesterol transport [44]. Once in the mitochondria, cholesterol is converted to pregnenolone by the cytochrome P450 side-chain cleavage enzyme [45]. Then, pregnenolone can be transferred out of the mitochondria and converted into the different steroids, including estrogen, by specific microsomal P450 enzymes [46].

Estrogen: From Brain Development to Brain Aging

Today, it is recognized that the action of estrogen is not limited to the regulation of endocrine functions and behaviour. Estrogen plays predominant roles as pleiotropic factor in the development and function of the CNS. Numerous evidence highlighted the influence of both male and female sex hormones on neural circuit development, sex-specific behaviours and sexual differentiation of mammalian brain from the foetal-neonatal

period to puberty and adult life (reviewed in [47]). For instance, the transition from childhood to adulthood is marked by morphological changes in the brain that are associated with sex hormone levels [48]. Interestingly, the structure and function of the brains of female and male animals as well as humans have been demonstrated to be markedly different in the number of cells in specific brain areas [49]. This gender dimorphism in several areas of the brain appears to be dependent on the action of gonadal hormones as variations in the volume of cortical and sub-cortical regions were correlated to the levels of estrogen and testosterone during puberty [49,50].

Interestingly, the group of Shah showed that the conversion of testosterone to estradiol by the enzyme aromatase is necessary during the perinatal period for the expression of masculine sex behaviour in the adult, while the absence of testosterone and estrogen is necessary for normal development of female brains [51]. This points out the importance of brain estrogen synthesis in aromatase-expressing neurons during foetal male life. Although testosterone is important for male development and behaviour throughout life, it is now recognized that estrogen plays also important roles in the male brain (reviewed in [7]).

Estrogen can induce several effects through different pathways (see also next section). The identification of estrogen receptors (ER) outside their classical CNS regions like the hypothalamus and the pituitary gland justifies their role in controlling different brain functions [8]. This organizational effect is firstly acting during the foetal-neonatal period where estrogen modulates neuronal development and the development of neuronal circuits [52]. Brain plasticity begins with the formation of the nervous system during early development and continues through the puberty, reproduction and adult life [53]. Estrogen seems to be also important for the maintenance and regulation of the network integrity of brain areas related to cognition, especially the hippocampus and associated structures [54]. In peri- and postmenopause, neurosteroids including estrogen undergo important changes due to the disturbance of gonadal hormone production and many CNS functions associated with

hippocampal activities deteriorate, such as memory, cognition and attention [55].

Estrogen Pathways: Estrogen Receptors, BDNF and Sirtuin 3

Different pathways play a role in the pleiotropic effects of estrogen in the brain. In the following, we discuss the emerging evidence about the role of ER and the estrogen - brain-derived neurotrophic factor (BDNF) as well as estrogen - sirtuin 3 (SIRT3) pathways that converge on the mitochondria.

Estrogen Receptors

Among the sex steroid hormone receptors, ERα and ERβ have been shown to be localized in mitochondria depending on the cell type and they ensure the mitochondrial function. The co-localization of ERβ and mitochondrial markers have been demonstrated in rat primary neurons and a murine hippocampal cell line suggesting a role of mitochondrial ERβ in mediating estrogen effects [56] (Figure 2). Indeed, ERβ is described as the type of ER that is most frequently present in mitochondria in most cell types [57]. ERα seems also to play a role, since estrogen exerted protective effects in human cerebral endothelium by increasing mitochondrial cytochrome *c* protein and mRNA, as well as reducing ROS through ERα but not ERβ receptors [58].

In addition, estrogen response elements (ERE) are present in the mtDNA and allow the binding of steroid receptors. In fact, ER can bind to ERE located in the mtDNA [59]. This association is known to improve the expression of mitochondrial-encoded genes and the ETC activity (Figure 2) [60]. Moreover, sex steroid hormone receptors have been suggested to bind mitochondrial proteins. Indeed, the association of mitochondrial ERβ with mitochondrial respiratory complex proteins was investigated in a series of co-immunoprecipitation studies showing that ERβ can interact with the respiratory complex V [3,61]. In different brain areas, there is a differential expression of mitochondrial ERα and ERβ variants suggesting that they can

participate in several functions in the brain during aging [61]. In female rats, mitochondrial ERα and ERβ were detected in the hypothalamus, cortex and hippocampus with no difference between young (3 months old) and aged (18 months old) animals [61].

Sirtuin 3 Pathway

The function of the sirtuin family consisting of seven members is important in different aspects of cellular regulation such as lipid homeostasis and metabolism (reviewed [62]), apoptosis resistance (reviewed in [63]) and oxidative stress management (reviewed in [64]). In addition, sirtuins are believed to contribute to the aging process and may play direct roles in longevity regulation [65]. Among the sirtuin members, sirtuin 3 (SIRT3) has received much attention for its role in aging and neurodegenerative diseases and is reported to affect human lifespan (Reviewed in [66]). SIRT3 is one of the three genomically expressed sirtuins that localize to mitochondria [67,68] as well as the primary mitochondrial protein deacetylase [69]. SIRT3 controls energy demand during stress conditions including oxidative stress conditions related to the aging process (Figure 2) (Reviewed in [66]). In addition, its over-expression prevented neuronal derangements in certain *in vitro* and *in vivo* models of aging [70], whereas its knockout in *Sirt3*$^{-/-}$ mouse embryonic fibroblasts induced abnormal mitochondrial physiology as well as increases in stress-induced superoxide levels and increased genomic instability [71]. At the mRNA level, *Sirt3* is the third most expressed member of the sirtuin family in the whole brain of the adult rat, except in the cerebellum where its expression was modestly lower [72]. During the development, mRNA expression pattern of *Sirt3* was similar in cortex, cerebellum and hippocampus, with *Sirt3* mRNA levels being fairly consistent from embryonic day 18 (E18) until 24 months of age [72]. Unfortunately, gender differences were not investigated in the study of Sidorova-Darmos [72], since the gender was not specifically determined for E18, postnatal days (PN) 2, PN7 or PN21 stages, while only female rats were used for the 3 and 24 month tissue samples, but *Sirt3* mRNA levels were similar at least in liver tissue from male

and female mice at the age of 11 months [73]. Braidy and co-workers investigated changes in the protein levels of various sirtuins in the aged female rat brain. 24 months old rats showed lower SIRT3 levels in the hippocampus and frontal cortex, but not occipital or temporal lobe, compared to 3 months old rats [74].

The co–presence of SIRT3 and the peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) implicates its role in mitochondrial biogenesis that provides ATP to support fundamental cellular processes involved in synaptic plasticity such as neurite outgrowth [75]. Interestingly, the mitochondrial SIRT3 promoter region carries an estrogen-related receptor (ERR)-binding element (ERRE) located 399- to 407-bp downstream (Figure 3) [75]. SIRT3 attenuates ROS and protects the cell from ROS both directly through the deacetylation of manganese superoxide dismutase (MnSOD) (Figures 2 and 3) and indirectly via interaction with transcription factors such as forkhead box O3 (FOXO3a) (Figure 3) as demonstrated in TCam-2 cells [76]. Sirt3-induced activated FOXO3a translocates to the nucleus and augments FOXO3a-dependent antioxidant defense mechanisms, through upregulation of PGC-1α and MnSOD (Figure 3).

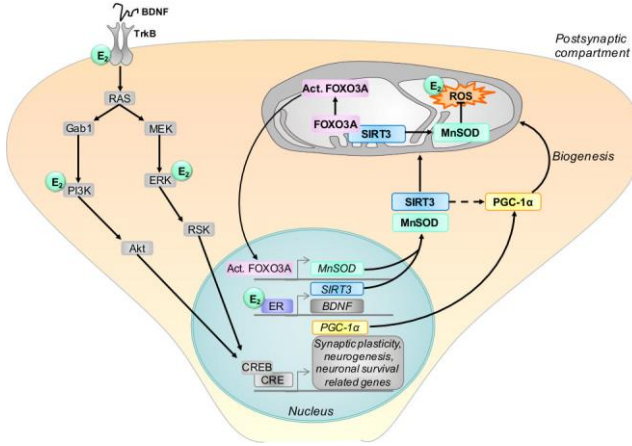

Figure 3: Model of possible interactions between estrogen, BDNF and sirtuin 3.

BDNF protein binds to its tyrosine kinase B receptor (TrkB) which stimulates signaling pathways, including the extracellular signal-regulated kinase (ERK) and the phosphatidylinositol 3-kinase (PI3K) pathways. This leads to the activation of the cAMP response element-binding protein (CREB) and transcription of genes, including peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). Estrogen (E2) activates similar signaling pathways as BDNF, and, by binding its receptor (ER), modulates the gene expression of BDNF, TrkB and SIRT3. SIRT3 protein translocates to mitochondria and interacts with Forkhead box O3 (FOXO3A), thereby activating this protein. In turn, activated FOXO3A (Act. FOXO3A) induces the transcription of the manganese superoxide dismutase (MnSOD) which acts as ROS scavengers in mitochondria. In addition, SIRT3 protects the cell from reactive oxygen species directly through the deacetylation of MnSOD. SIRT3 regulates also the expression of PGC-1α (indicated by the doted arrow) which is involved in mitochondrial biogenesis. In the graph, E2 designates where estrogen may interact with the BDNF and SIRT3 pathways. BDNF: brain derived neurotrophic factor, CRE: cAMP response elements, PGC-1α: proliferator-activated receptor gamma coactivator 1-alpha, SIRT3: sirtuin 3

BDNF Pathway

Research has implicated one of the neurotrophic factors, BDNF, to be involved in age-related cognitive decline. A hypothesis has emerged that aging is associated with a decreased BDNF signaling capacity in the CNS [77]. In humans, BDNF levels have been shown to decrease in brain regions involved in age-related neurodegenerative diseases: e.g.; in Alzheimer's disease (AD) in the frontal cortex [78], the hippocampus [79], the

parietal cortex [80], and the entorhinal cortex [81]. However, age-related changes in brain BDNF levels in elderly humans during normal cognitive aging are under-investigated. In aged monkeys (26, 30, and 32 years), the intensity of BDNF-immunoreactivity has been found to decline in cell bodies and dendrites of the neurons in the hippocampal formation [82]. In humans, BDNF levels in plasma have been found to decrease with increasing age [83-85] and the levels of tropomyosin **receptor** kinase B (trkB, BNDF receptor) mRNA decreased over the life span [86]. In accordance with these results, it has been shown that the levels of trkB decrease in the rat hippocampus during aging [87,88] and 24-month-old rats exhibited significantly less BDNF protein in three brain regions as compared to 4-month-old rats [89]. However, it should be noticed that conflicting data from animal research exist not always confirming whether age-related changes do occur in the brain ([89]. Compared to females, males had lower BDNF levels in the hippocampus at 20 months emphasizing the important role of gender and sex hormones [89]. Therefore, discordant findings between aging studies may also be related to the fact that some studies used males (e.g., [90,91], whereas others used female animals (e.g., [92]. In agreement with these findings, some authors found that elderly females, but not elderly males, with poorer cognitive performance had lower plasma BDNF levels than better performers (e.g., [93]) and smaller hippocampal volumes are associated with reduced levels of serum BDNF and poorer memory performance [85]. Moreover, genetic studies have identified a single nucleotide polymorphism on the BDNF gene that moderates age-related cognitive decline [94]. Of note, a very recent study showed that estrogen tweaks circuit function by interacting with a uniquely human version of the gene that encodes for BDNF, the Val66Met genotype [95]. The BDNF Val66Met variant and ovarian steroids interactively modulate working memory-related hippocampal function in women suggesting that hormone-gene interaction may underlie sex/individual differences in brain disorders, thus providing a potential explanation for observations of individual differences in the effects of estrogen on hippocampal performance in women [95].

In summary, there is evidence suggesting that the BDNF-trkB system, especially in the hippocampus, is sensitive to aging and is modulated by gender and sex hormones respectively. In this context, the drop in estrogen in females during perimenopause might play a role in the cognitive function decline during female aging.

BDNF and estrogen are both important modulators of synaptic plasticity (Figure 3) [96]. Synaptic plasticity, the dynamic regulation of synaptic mechanisms like LTP (long-term potentiation), spine density and form, number and length of dendrites and axons (neuritogenesis) and the number of neurons (neurogenesis and apoptosis) represent major mechanisms by which our brain can adapt to periods of pathologically enhanced or reduced function or to save information at the synaptic level. Mitochondria play a crucial role as they provide the cellular energy for these adaptive responses or initiate apoptosis in case of neuronal damage beyond the possibility of repair. Changes of synaptic function and plasticity play a major role for cognitive deficits in aging and age-related brain disorders [97,98].

Activation of the high-affinity BDNF receptor TrkB results in phosphorylation of tyrosine residues in the cytoplasmic domain of the receptor and subsequent recruitment and activation of signaling proteins that engage extracellular signal-regulated kinases (ERKs) and the phosphatidylinositol 3-kinase (PI3K)-Akt kinase pathway (Figure 3) [99].

Notably, it has been shown that estrogen and BDNF receptor (trkB) coexpression leads to convergence of their signaling pathways (Figure 3) [100] and PI3K and MAPK/ERK protein cascades may be activated by estrogen or BDNF-bound membrane receptors [101]. Both pathways phosphorylate the transcription factor cAMP response element-binding protein (CREB) which, in turn, induces the expression of PGC-1α resulting in protein transcription, neuronal plasticity and memory formation and consolidation [102]. Intra-pathway crosstalk is in addition possible. Moreover, estrogen and BDNF can interact directly, because estrogen induces BDNF gene expression, which in turn acts on trkB to exert its effects (Figure 3) [100].

Induction of this kind may occur by an ERE on the BDNF gene or by estrogen-induced increase in neural activity that upregulates BDNF (Figure 3) [96,100]. By enhancing the uptake of energy substrates, mitochondrial biogenesis, and protein synthesis capabilities of neurons, estrogen-BDNF signaling plays pivotal roles in the adaptive changes in synapse formation and modification. Thus, the concerted action between BDNF and estrogen is important for the improvement of synaptic function and plasticity in aging.

Estrogen and Bioenergetics in Female Brain: Implications for Estrogen Replacement Therapy

Estrogen is an essential regulator of the metabolic system of the female brain and contributes to processes within the entire bioenergetic system including glucose metabolism, glucose transport and ATP production as well as mitochondrial respiration (Figure 2) [103]. A decline of 15-25% in metabolic function in the brain was observed after the loss of estrogen by surgical removal of ovaries or reproductive endocrine aging [104,105]. Recent research of our group confirmed *in vitro* the effects of estrogen on mitochondrial function (Figure 2). We showed that estrogen, such as estradiol and estrone, was able to improve bioenergetics and antioxidant defenses in primary neuronal cultures and in human neuroblastoma cells (SH-SY5Y) by increasing mitochondrial membrane potential, ATP levels, basal respiration, and MnSOD activity [106] (Figure 2). Besides, a treatment with estrogen was efficient in reducing bioenergetic impairments observed in a cellular model of AD [16,107]. Thus, estrogen represents an attractive therapeutic tool to counteract the mitochondrial impairments in aging and age-related disorders.

Female gender is the major risk factor for AD after advanced age. Preclinical studies demonstrated that the perimenopause to menopause transition is a sex-specific risk factor for AD [108]. In animal studies, estrogenic regulation of cerebral glucose metabolism falters during perimenopause [108]. During aging, a decline of genes required for mitochondrial function and β-

amyloid degradation was observed in a rat model recapitulating fundamental characteristics of the human perimenopause [109]. Impaired synaptic function and emergence of glucose hypometabolism in brain give plausible mechanisms of neurological symptoms of perimenopause and can be predictive of later-life vulnerability to hypometabolic conditions like AD [109].

In the metabolic system of the aging female brain, the earliest change is the persistent decline in neuronal glucose transport and metabolism, followed by a drop in mitochondrial function [110]. In fact, immediately before the transition into reproductive senescence, a hypometabolism in the brain of female mice (at 6-9 months) was demonstrated by a reduction in glucose uptake and hexokinase activity [110]. These phenomena were also accompanied by inactivation of complex IV activity and pyruvate dehydrogenase leading to an impairment of the mitochondrial energy-conservation system in the brain of female mice [110]. In parallel to the decline in glucose transport, lactate transport and utilization were also reduced, suggesting that the lactate is not used as an alternative fuel source during the transition to reproductive senescence.

Earlier preclinical findings indicating emergence of bioenergetic deficits in perimenopausal and postmenopausal women were recently validated and suggested that the optimal window of opportunity for therapeutic intervention in women is early in the endocrine aging process [108]. A study bridged basic to clinical science to characterize brain bioenergetics in a cohort of forty-three, 40±60 year-old clinically and cognitively normal women at different endocrine transition stages including premenopause, perimenopause and postmenopause. Compared to premenopause, both perimenopause and postmenopause groups exhibited a reduction in mitochondrial COX activity which was correlated with a decline of cerebral glucose metabolism in AD-vulnerable regions. A gradient in biomarker abnormalities correlated with immediate and delayed memory scores and was most pronounced in post-menopause, intermediate in perimenopause, and lowest in premenopause [108]. Therefore, estrogen replacement therapies (ERT) may only be beneficial before

women accumulate a certain threshold of cellular damage, at the appropriate time of a woman's life, also known as the "critical period" that starts during perimenopause and ends early after menopause (Figure 1) [10,17,111]. This "critical period" might also explain the failure of the Women's Health Initiative (WHI) study including only postmenopausal aged over 68 years thereby missing the vulnerable time frame [112,113].The window of opportunity concept supports that estrogen can have beneficial effects only on healthy brain during the years before the menopause compared to some years after the menopause onset where ERT could even present detrimental effect on brain activity [103,114-118]. The effectiveness of ERT is also dependent on the formulation of treatments (e.g. use of synthetic conjugated equine estrogen versus natural estrogen, or co-treatment with progesterone), the mode of delivery (transdermal or oral) and the regimen (cyclic or continuous) [118].

Importantly, recent evaluation of the role of estrogen showed that hormonal therapy can prevent the deleterious effects of aging in cognition, and decreases the risks of dementia, if initiated early [119]. In this context, beneficial treatment effects of estrogen might be mediated by the BDNF and SIRT3 pathways and their convergence via PGC-1α on mitochondria (Figure 4).

Conclusion

Over the last decade, accumulating evidence has suggested a causative link between mitochondrial dysfunction and major phenotypes associated with aging. A number of recent studies link mitochondrial function to signaling pathways that regulate brain plasticity, life span and to the aging process. It is clear that estrogen exerts actions on the mitochondria and that these organelles play an important role in age-related processes. In this context, estrogen/BDNF or estrogen/SIRT3 actions and interactions represent complex and fundamental mechanisms of neuronal plasticity, a process highly depending on energy supply via mitochondrial activity (Figure 4). Notably, a growing body of evidence indicates emergence of bioenergetic deficits already in perimenopausal women, suggesting that the optimal window

of opportunity should be used for the therapeutic intervention in women during the endocrine aging process.

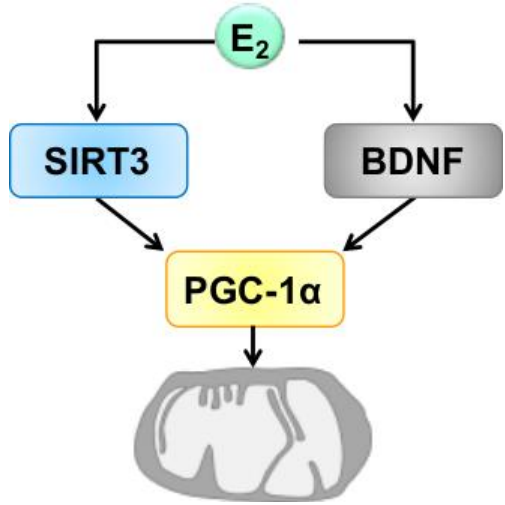

Figure 4: Hypothetic model of the convergence of BDNF and SIRT3 on mitochondria induced by estrogen.
Estrogen (E2) induces the expression of BDNF and SIRT3. The action of BDNF and SIRT3 converges on mitochondria by regulating the expression of PGC-1α which is involved in mitochondrial biogenesis that is necessary for synaptic plasticity. BDNF: brain derived neurotrophic factor, PGC-1α: proliferator-activated receptor gamma coactivator 1-alpha, SIRT3: sirtuin 3

A full understanding of the molecular mechanisms triggered by estrogen at the mitochondrial level and its effects in aging populations may provide profound and exciting possibilities for the future treatment of age-dependent diseases associated with the deregulation of sexual hormone levels.

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