



# Estrogen Interactions With Lipid Rafts Related to Neuroprotection. Impact of Brain Ageing and Menopause

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Estrogens (E2) exert a plethora of neuroprotective actions against aged-associated brain diseases, including Alzheimer's disease (AD). Part of these actions takes place through binding to estrogen receptors (ER) embedded in signalosomes, where numerous signaling proteins are clustered. Signalosomes are preferentially located in lipid rafts which are dynamic membrane microstructures characterized by a peculiar lipid composition enriched in gangliosides, saturated fatty acids, cholesterol, and sphingolipids. Rapid E2 interactions with ER-related signalosomes appear to trigger intracellular signaling ultimately leading to the activation of molecular mechanisms against AD. We have previously observed that the reduction of E2 blood levels occurring during menopause induced disruption of ER-signalosomes at frontal cortical brain areas. These molecular changes may reduce neuronal protection activities, as similar ER signalosome derangements were observed in AD brains. The molecular impairments may be associated with changes in the lipid composition of lipid rafts observed in neurons during menopause and AD. These evidences indicate that the changes in lipid raft structure during aging may be at the basis of alterations in the activity of ER and other neuroprotective proteins integrated in these membrane microstructures. Moreover, E2 is a homeostatic modulator of lipid rafts. Recent work has pointed to this relevant aspect of E2 activity to preserve brain integrity, through mechanisms affecting lipid uptake and local biosynthesis in the brain. Some evidences have demonstrated that estrogens and the docosahexaenoic acid (DHA) exert synergistic effects to stabilize brain lipid matrix. DHA is essential to enhance molecular fluidity at the plasma membrane, promoting functional macromolecular interactions in signaling platforms. In support of this, DHA detriment in neuronal lipid rafts has been associated with the most common age-associated neuropathologies, namely AD and Parkinson disease. Altogether, these findings indicate that E2 may participate in brain preservation

through a dual membrane-related mechanism. On the one hand, E2 interacting with ER related signalosomes may protect against neurotoxic insults. On the other hand, E2 may exert lipostatic actions to preserve lipid balance in neuronal membrane microdomains. The different aspects of the emerging multifunctional role of estrogens in membrane-related signalosomes will be discussed in this review.

**Keywords: menopause, estrogen receptors, estrogen, lipid rafts, neurodegeneration, signalosome**

## GENERAL OVERVIEW

Sex steroids produced by peripheral glands such as dihydrotestosterone (DHT), testosterone (T), estradiol (E2), progesterone (PROG), and corticosterone (CORT) are traditionally known to play crucial roles in sexually dimorphic circuits located in the hypothalamus and other brain areas controlling reproductive behaviors, as well as brain masculinization, brain connectivity, and neuroplasticity (Losecaat Vermeer et al., 2016; Panzica and Melcangi, 2016). Furthermore, the central and peripheral nervous systems show local synthesis of neurosteroids (Melcangi et al., 2008; Giatti et al., 2010). These neuroactive steroids are considered important regulators of neural functions, including brain and cerebellar development, hippocampal neurogenesis and synaptogenesis (Murakami et al., 2017), and neuroprotection against numerous pathologies, such as Alzheimer's disease (AD), Parkinson disease (PD), Huntington's disease (HD), stroke, multiple sclerosis (MS), spinal cord injury, peripheral neuropathy, and psychiatric disorders (Melcangi et al., 2016). These disorders show gender differences in their incidence and progression, as an indicative of the different roles of neurosteroids in the physiological actions in the nervous system. Indeed, sex hormones also influence the local concentrations of neurosteroids that affect the pathological context. Thus, epidemiological studies have demonstrated a higher incidence in women of AD, HD, MS, peripheral neuropathy, and some psychiatric disorders, such as anxiety, depression, and eating disorders. In the contrary, men show a higher incidence of PD, stroke and autism as compared to women (Andersen et al., 1999; Wooten et al., 2004; Afifi, 2007; Reeves et al., 2008; Melcangi et al., 2016). In particular related to AD, neuroprotective effects of estrogens in either cellular, animal, and clinical studies have been extensively studied and characterized, whereas brain beneficial actions of androgens and stress steroids have been less investigated, and require further clarification of the common molecular mechanisms of neurosteroid effects. Interestingly, the incidence of AD in men does not seem directly related to estrogens, since estrogens in men do not exhibit a reduction with aging. Rather, detriment in testosterone levels in men brain may predict enhanced vulnerability to AD (Moffat et al., 2004; Pike, 2017). This phenomenon appears to be sex-specific, since testosterone levels do not show significant changes in women suffering AD (Rosario et al., 2011).

A general clinical observation is that menopausal women show a higher risk of developing a neurodegenerative disease,

indicating that estrogens are neuroprotective. Numerous data in the last decade have concluded that estrogens (E2) exert a plethora of neuroprotective actions against aged-associated brain diseases, including AD. Part of these actions takes place through binding to estrogen receptors (ER) embedded in signalosomes, where numerous signaling proteins are clustered. Signalosomes are preferentially located in lipid rafts which are dynamic membrane microstructures characterized by a peculiar lipid composition enriched in gangliosides, saturated fatty acids, cholesterol, and sphingolipids. Rapid E2 interactions with ER-related signalosomes appear to trigger intracellular signaling ultimately leading to the activation of molecular mechanisms against AD.

We have previously observed that the reduction of E2 blood levels occurring during menopause induced disruption of ER-signalosomes at frontal cortical brain areas. These molecular changes may reduce neuronal protection activities, as similar ER signalosome derangements were observed in AD brains. The molecular impairments may be associated with changes in the lipid composition of lipid rafts observed in neurons during menopause and AD. These observations indicate that the changes in lipid raft structure during aging may be at the basis of alterations in the activity of ER and other neuroprotective proteins integrated in these membrane microstructures.

Moreover, E2 is a homeostatic modulator of lipid rafts. Recent work has pointed to this relevant aspect of E2 activity to preserve brain integrity, through mechanisms affecting lipid uptake and local biosynthesis in the brain. Some findings have demonstrated that estrogens and the docosahexaenoic acid (DHA) exert synergistic effects to stabilize brain lipid matrix. DHA is essential to enhance molecular fluidity at the plasma membrane, promoting functional macromolecular interactions in signaling platforms. In support of this, DHA detriment in neuronal lipid rafts has been associated with the most common age-associated neuropathologies, namely AD and Parkinson disease.

Altogether, these findings indicate that E2 may participate in brain preservation through a dual membrane-related mechanism. On the one hand, E2 interacting with ER related signalosomes may protect against neurotoxic insults. On the other hand, E2 may exert lipostatic actions to preserve lipid balance in neuronal membrane microdomains. The different aspects of the emerging multifunctional role of estrogens in membrane-related signalosomes will be discussed in this review.

## Neurological Transition During Menopause

Perimenopause and menopause are important periods of woman's life where significant physiological changes occur. Perimenopause is a period in women whose age range is between 40–58 years, followed by a transition period of 1–5 years that culminates with ~12 months of amenorrhoea (Harlow et al., 2012). Menopause is the final stage associated with cessation of ovarian secretion of female sex hormones, estrogen, and progesterone (Greendale et al., 2013). It is calculated that, within EEUU and Europe, ~ >176 million women undergo menopausal periods, and this number increases by 9 million per year. Moreover, worldwide, it is estimated that there are >850 million women in perimenopause stages (Brinton et al., 2009). Even more, only 20% of women are asymptomatic during this process, whereas the remaining 80% suffer different symptoms associated with hormone detriment.

Even though perimenopausal stages are focused on changes in the reproductive system by oocyte depletion (hot flushes, vaginal dryness, fatigue, irregular periods, etc.), the majority of symptoms of these periods are neurological in nature (Brinton et al., 2015). These features are variable, and appear to be coincident with a decline of brain metabolism (Rasgon et al., 2005). The most common neurological disturbances reported are insomnia, mood changes, depression, subjective memory complaints, and cognitive dysfunction (specifically learning and memory impairments).

Several studies have documented that women show higher protection against the nervous system pathologies as compared with men, whereas this tendency is inverted after menopause (Sherwin and Henry, 2008; Pike, 2017). Consequently, it is plausible that falling estrogen levels during menopausal periods may increase the risk of neuronal vulnerability against injury. In agreement with this, ovariectomy before natural menopause is correlated with a higher incidence of dementia and PD (Rocca et al., 2008). Also, premature menopausal women show a higher risk of AD (Ryan et al., 2014). Furthermore, numerous evidence has agreed that the progression of menopause increases the incidence of neurological perturbations associated with the most common aged-related neurodegenerative diseases, such as AD, and PD, as well as cerebral stroke, ischemia and multiple sclerosis (Ramagopalan et al., 2010; Schreihofner and Ma, 2013; Picillo et al., 2017; Pike, 2017).

Besides gonadal hormone detriment in menopause, synthesis of estrogens at, both, central and peripheral nervous systems may also be affected with the progression of aging (Melcangi et al., 2008; Giatti et al., 2015). Thus, neurosteroidogenesis is decreased during menopause (Rosario et al., 2011), and this reduction is exacerbated in AD brains (Schumacher et al., 2003). Furthermore, the link between estrogen loss in post-menopausal women and the risk of dementia is supported by clinical evidence reporting that the incidence of AD is 2–3 times higher in women than in men (Ryan et al., 2014). Overall, multifactorial variations of estrogenic production in, both, gonadal and nervous system during menopausal periods may intervene in the resulting neurological impairments. Moreover, these data reflect the importance of developing novel accurate hormonal replacement strategies to counteract the potential cognitive decline related

to menopause, despite the inconclusive and discouraging results obtained in previous clinical trials (Merlo et al., 2017).

## Estrogens Protect the Brain

Estrogens display a variety of physiological roles in the brain, including neuronal differentiation, neurogenesis, and neuronal plasticity, which are crucial for brain homeostasis, cognition, and preservation (Brinton, 2009; Engler-Chiurazzi et al., 2017). In addition, E2 regulates actions on glial cells at, both, central and peripheral nervous system (CNS and PNS) including oligodendroglia, astrocytes, and microglia (CNS), and Schwann cells (PNS). These hormone actions include remyelination, inflammation, edema formation, and extracellular glutamate levels which are important in the regulation of physiological homeostasis, and preservation against pathophysiological situations (Arevalo et al., 2010). Different data has reported that Schwann cells, oligodendrocytes and astrocytes are targets of E2. Thus, the hormone enhances myelin sheet formation and the synthesis of myelin basic protein through direct actions in Schwann and oligodendroglial cells (Jung-Testas et al., 1992, 1993; Fex Svenningsen and Kanje, 1999; Marin-Husstege et al., 2004). E2 also regulates the morphology of astrocytes as well as the expression of numerous molecules involved in the regulation of astrocytic functions (Luquin et al., 1993; Garcia-Segura et al., 1996; McCarthy, 2008). Furthermore, E2 modulates microglial response to inflammation, thus avoiding overreaction of these cells following brain injury (Vegeto et al., 2006; Tapia-Gonzalez et al., 2008).

Taking into account these data, it is plausible to affirm that menopause-related alterations in the nervous system may be highly associated with estrogen depletion and estrogen receptors (ERs) regulation. A big body of data has reported a number of mechanisms by which estrogens (in particular, 17 $\beta$ -estradiol, E2) protect against different neuroinflammatory and neurodegenerative disorders. Thus, E2 has been demonstrated to exert beneficial actions against a wide range of diseases: AD, PD, ischemia, schizophrenia, multiple sclerosis, hypertensive encephalopathy, spinal cord injury, traumatic brain injury, and retinal degeneration (De Nicola et al., 2012; Petrone et al., 2014; Cascio et al., 2015; Lan et al., 2015; Brotfain et al., 2016; Itoh et al., 2017; McGregor et al., 2017; Raghava et al., 2017). Furthermore, a plethora of *in vivo* and *in vitro* studies over more than two decades have provided evidence that estrogen exerts beneficial effects against different insults (Brann et al., 2007; Petrovska and Jurisic, 2012). Among other toxic paradigms, it has been documented that estrogens protect neurons against glutamate excitotoxicity, glucose and serum deprivation, stress injury, hydrogen peroxide, iron, sodium azide, and A $\beta$ - and MPTP-induced toxicities (Siddiqui et al., 2016). In addition, E2 contributes to modulate the decrease in gliotic responses under neurodegenerative conditions, through different actions including glial cell proliferation after brain injury (Garcia-Estrada et al., 1993; Zhang et al., 2002; Vegeto et al., 2006). In particular in AD, E2 enhances A $\beta$  uptake by microglia, as a mechanism to promote A $\beta$  clearance (Li et al., 2000; Yue et al., 2005).

The precise molecular mechanisms underlying E2 neuroprotective effect still remain elusive because of the vast complexity of the brain. Even though some of these actions may be explained by the intrinsic antioxidant properties of this hormone, acting as free radical scavenger of oxidative stress (Prokai et al., 2003), the majority of E2 neuroprotective effects require binding to ERs. To date, three distinct ERs have been characterized distinctly distributed throughout the different brain areas: ER $\alpha$ , ER $\beta$ , and G-protein coupled ER1 (GPER) (Prossintz and Barton, 2011; Lu and Herndon, 2017). In addition, a variety of splice variants of ER $\alpha$  and ER $\beta$  (ranging from 36 to 80 kDa) has also been identified in different systems, although its functional relevance in brain preservation is still unclear (Ascenzi et al., 2006; Marin et al., 2006; Kim et al., 2017). Interestingly, certain of these splice forms are brain-area specific. In this sense, an ER $\alpha$ -splice variant (MB1) has been shown to increase its expression in women brains during the transition period to menopause, as an indicator of their potential role during aging (Ishunina and Swaab, 2008).

Furthermore, ER $\alpha$  and ER $\beta$  have also been detected in glial cells. Thus, some immunohistochemical assays have demonstrated an abundant localization of ERs in glial cells of rat and mouse brain (Cardona-Gómez et al., 2000; Quesada et al., 2007; Sierra et al., 2008; Tapia-Gonzalez et al., 2008). Both ERs show partially distinct distribution in neural tissues, suggesting that they may have distinct or complementary actions that modulate glial responses related to remyelination, anti-inflammatory process, edema formation, and other reparative mechanisms (Arevalo et al., 2010). Thus, ER $\beta$  participates in preservation of axonal integrity and demyelination in oligodendrocytes (Tiwari-Woodruff and Voskuhl, 2009), and against ischemia in microglia in the hippocampus (Takahashi et al., 2004). Expression of this receptor in oligodendroglia has also been recently shown to play a role in optic glioma-induced retinal dysfunction (Toonen et al., 2017). Furthermore, ER $\alpha$ , but not ER $\beta$ , expressed in oligodendrocytes plays anti-inflammatory actions in an animal model of multiple sclerosis (Tiwari-Woodruff et al., 2007). ER $\alpha$  has also been detected in microglia from mouse adult brain and rat cerebellum following peripheral inflammation (Sierra et al., 2008; Tapia-Gonzalez et al., 2008). Moreover, both receptors play a role throughout neural tissue maturation showing a differential expression in astrocytes and oligodendrocytes in the spinal cord during rat development (Platania et al., 2003). Collectively, these results suggest that glial cells utilize E2 bound to ERs to influence reparative mechanisms within microenvironments in the brain and SNP.

## MULTIFACTORIAL ROLES OF ESTROGEN RECEPTORS IN BRAIN PRESERVATION

ERs are widely distributed in different brain areas. These receptors are highly expressed in the hypothalamus, which is a primary center regulator of body temperature, sleep, and circadian rhythms (McEwen et al., 2012). ERs are also

shown in important regions for memory, cognition, attention, sensory integration, mood, emotion, and motivation, such as the prefrontal cortex, hippocampus, amygdala, posterior cingulate, thalamus, raphe nucleus, and locus coeruleus (McEwen et al., 2012; Brinton et al., 2015; Hara et al., 2015). The distribution patterns of ER $\alpha$  and ER $\beta$  are distinct, observing higher levels of ER $\alpha$  in hypothalamus and amygdala, whereas ER $\beta$  is most abundant in the thalamus and hippocampus (Osterlund et al., 2000a,b), as an indicative of different roles developed by these receptors in the brain.

The neurobiological circuits expressing ERs are affected during the perimenopausal transition, in co-incidence with the most common neurological symptoms of perimenopausal periods. Brain changes in ER patterns have been investigated in aged female primates as a valuable model for studying the menopause-related alterations that may affect brain functionality (Gilardi et al., 1997; Walker and Herndon, 2008). During menopause in rhesus monkey females, a lower density of synapse spines, and changes in synapsis structure have been observed, in particular, in the hippocampal dentate gyrus and prefrontal cortex (Hara et al., 2015). These changes were correlated with lower memory performance, whereas the cognitive skills were recovered by estrogen treatment in the menopausal monkeys (Hara et al., 2014). Reduction in hippocampal synaptic density was also observed in a mouse model of menopause (Van Kempen et al., 2014), suggesting a role of E2 in neuronal plasticity.

A high number of evidence has demonstrated that E2 bound to its receptor follows different pathways that are subjected to multifactorial extracellular and intracellular events. With the exception of GPER that binds to the hormone at the plasma membrane, ER $\alpha$  and ER $\beta$  are dynamic molecules that have been shown to be located within distinct neuronal and glial compartments suggesting the co-existence of different intracellular mechanisms of E2 action (Milner et al., 2001; Pawlak et al., 2005; Ogiue-Ikeda et al., 2008). In the cellular nucleus, E2 binding to ERs induces in a few hours genomic (or classical) mechanisms of action, leading to the transcriptional activation of late response genes that regulate, among others, apoptosis, and inflammation (Marin et al., 2005; Heldring et al., 2007). Other ERs, ER $\beta$  in particular, are found in mitochondria, contributing to maintain mitochondrial functionality (Nilsen et al., 2007; Yang et al., 2009). In these organelles, E2 acts as regulator of bioenergetics circuits (Brinton, 2008), counteracting the oxidative stress and glucose hypometabolism etiologies implicated in AD and PD, as well as amyotrophic lateral sclerosis (ALS) (Simpkins and Dykens, 2008).

Furthermore, a wide variety of neuroprotective actions has been shown to occur within seconds to minutes following E2 exposure. These actions are referred to as rapid or non-genomic mechanisms, where plasma membrane-associated ERs binding to the hormone are involved (Pietras and Szego, 1977; Levin, 2009). These non-genomic mechanisms promote the rapid activation of different intracellular signaling pathways that ultimately may lead to neuroprotection. The best characterized pathway in neurons involves the activation of extracellular signal-regulated kinases (ERK) and phosphatidylinositol 3-kinase (PI3K)/Akt/glycogen

synthase kinase 3 (GSK3) pathway in brain areas related to memory and cognition (Kelly and Levin, 2001; Marin et al., 2005; Garcia-Segura et al., 2006; Sheppard et al., 2017). In septal and hippocampal neurons, activation of PI3K/Akt/GSK3 signal transduction has been shown to protect against injuries induced by, A $\beta$  exposure, glutamate excitotoxicity, staurosporine-induced apoptosis, and oxygen glucose deprivation (Marin et al., 2005; Zhao et al., 2016). Apart from neuronal survival, this signaling pathway mediates cytoskeletal remodeling, synaptic plasticity, and traumatic brain injury (Garcia-Segura et al., 2007; Wang et al., 2017). Another preferential alternative intracellular pathway by E2 membrane interactions involve activation of Raf/MEK/ERK signaling, which enhances neuroprotection following ischemic brain injury, stroke and A $\beta$ - and glutamate-induced toxicities (Bryant et al., 2006; Lebesgue et al., 2009).

Although still not fully characterized, the generally held view maintains that these membrane-related mechanisms of E2 are modulated by cell membrane homeostatic mechanisms, where plasma membrane functional microdomains may play a preferential role.

## INVOLVEMENT OF NEURONAL LIPID RAFTS IN RAPID ESTROGEN SIGNALING

Lipid rafts are dynamic membrane microstructures enriched in distinct lipid classes, such as cholesterol, sphingolipids, saturated fatty acids, and gangliosides (Lingwood and Simons, 2010). This peculiar molecular composition confers particular physico-chemical properties, observing a higher molecular order and microviscosity as compared to non-raft membrane regions. Lipid rafts are regulators of signaling platforms (or signalosomes) formed by subsets of proteins that compartmentalize in multimolecular clusters to trigger different cellular responses (Levental and Veatch, 2016). The association of apparent hydrophobic proteins to lipid rafts typically takes place through association with different structural features or lipid moieties that confer stability to the molecular complexes. The most common protein anchoring targets in these microstructures are glycosylphosphatidylinositol (GPI), cholesterol, glycosphingolipids (GPL) S-palmitoylation, N-myristoylation/palmitoylation, and S-acylation with saturated fatty acids (Fantini, 2007; Levental et al., 2010). Moreover, the particular microstructure of these highly molecular-ordered domains may have consequences in the configuration of proteins embedded. The molecular rearrangements may favor the interaction of protein entities that co-exist in the same raft microdomain, thereby enhancing the formation of functional multiprotein clusters.

The subgroup of membrane-related ERs (mERs) classically represents a small fraction of the total amount of receptors within the cell. ER molecule lacks either transmembrane domains, hydrophobic residues or other structural modifications to be inserted into the plasma membrane (Pedram et al., 2007). Although the strategies developed by a subpopulation of ERs to anchor into the lipid bilayer are not yet fully clarified, some results in different cell types have demonstrated that

palmitoylation of the receptor is required to be trafficked to the cell membrane (Meitzen et al., 2013). This modification lies in the covalent attachment of palmitic acid and other fatty acids to a cysteine residue present in ERs to increase hydrophobicity. In particular, Cys447 located in the ligand binding domain has been demonstrated to be essential for ER $\alpha$  to interact with the cell membrane. Indeed, the replacement of this amino acid by Ala447 abrogates receptor insertion into the membrane compartment (Acconcia et al., 2005).

The other necessary requirement for membrane trafficking of ERs is their association with lipid rafts (Marin et al., 2012; Maselli et al., 2015). In these microdomains, ER $\alpha$  also appears to be palmitoylated (Liu et al., 2002). The stability of this receptor in lipid rafts is achieved by its interaction with caveolin-1, a raft scaffolding protein that allows ER $\alpha$  membrane anchoring (Boulware et al., 2007). In support of this, ER $\alpha$  primary structure shows a consensus sequence at positions 463–470 of the ligand binding domain susceptible of binding to caveolar scaffolding domain (CSD) present in caveolin-1 (Marin et al., 2008). This consensus motif is conserved in different proteins involved in signal transduction (Couet et al., 1997), and is required for the transport of signaling proteins into raft domains (Massimino et al., 2002). Furthermore, ER $\alpha$  downstream signaling may also involve other members of the caveolin family, such as caveolin-2 and -3, as demonstrated in neurons from different brain regions (Micevych and Mermelstein, 2008).

Lipid rafts provide the proper microenvironment for the recruitment and integration of a wide range of receptors within signaling platforms (signalosomes) that are activated upon specific extracellular stimulation, thereby inducing distinct cell responses. In this scenario, numerous lipid raft-associated proteins have been shown to be involved in nervous system functioning. The list includes GPI-anchored receptors; G protein-coupled receptors (adrenergic receptors, adenosine receptors and cannabinoid receptors); glutamate receptors (AMPA, NMDA, mGluR); neurotrophin receptors (tyrosine kinase receptors, TrkA, TrkB, ephrin receptor, Eph, c-Ret, ErbB); Src family receptors (c-Src, Lyn, Fyn); cell adhesion molecules (NCAMs, TAG-1, Thy-1); and proteins associated with myelin glycosynapse (LINGO1, p75, NgR1, myelin-associated glycoprotein). The association of this plethora of proteins in signalosomes has been shown to modulate synapsis, neuronal plasticity, cell-cell communication, myelin organization and stability, autophagy, neuronal survival, and neurodegeneration (George and Wu, 2012; Egawa et al., 2016). For an excellent review of the importance of the lipid raft-related protein classes in the brain context see Sonnino et al. (2014).

Several lines of evidence have demonstrated that ERs, ER $\alpha$  in particular, form part of raft-integrated signalosomes to initiate a variety of neuronal responses by mechanisms still not fully elucidated (Srivastava et al., 2011). Caveolin-1 has been shown to be the pivotal docking protein of ER $\alpha$ -related signalosomes in brain areas related to memory and cognition. Thus, caveolin scaffolding protein serves to determine interactions of ER with metabotropic glutamate receptors (mGluRs) in lipid rafts of the hippocampus and striatum (Meitzen and Mermelstein, 2011; Micevych and Kelly, 2012). E2 signaling initiated at the

membrane level by interaction with the pairing of mGluR and ER triggers intracellular responses that may be important for, both, neuronal and glial physiology. This membrane estrogen signaling occurs in the absence of mGluR-specific ligands, and represents one of the underlying mechanisms of rapid estrogen actions related to the nervous system functioning. Moreover, caveolin-1 is also the pivotal anchor of ER $\alpha$  interactions with the insulin growth factor-1 receptor  $\beta$  (IGF-1R $\beta$ ). This ER $\alpha$ /IGF-1R $\beta$  tandem has been shown to be cross-talked modulated by their natural ligands, E2 and IGF-1, which mutually cooperate in the prevention of age-related neuronal dysfunction (Alonso and Gonzalez, 2012; Arevalo et al., 2015), and are crucial in brain preservation against AD (Marin, 2011; Lan et al., 2015).

It has been postulated that part of E2 neuroprotective actions triggered in ER $\alpha$  signalosomes against A $\beta$  toxicity occur by the activation of different signal transduction pathways, including a voltage-dependent anion channel (VDAC) gating modulation. This channel appears associated with ER $\alpha$  in neuronal lipid rafts from a wide variety of brain regions, including septum, hippocampus, and cortex from, both, murine and human origins (Marin et al., 2007, 2009; Ramirez et al., 2009), where it participates in different pathogenesis including AD (Thinnes, 2015). In raft fractions of cortical neurons, VDAC interacting with A $\beta$  promotes the channel dephosphorylation in tyrosine residues, a phenomenon that promotes VDAC gating, and enhances neuronal death (Fernandez-Echevarria et al., 2014). Indeed, VDAC appears in a dephosphorylated status in cortical raft fractions of AD brains at late stages, as an indicative of the toxic post-transductional modification of the channel in correlation with the pathology (Canerina-Amaro et al., 2017). Conversely, E2 binding to ER $\alpha$  signalosome has been shown to prevent VDAC channel dephosphorylation in neurons, as a mechanism underlying cell survival against A $\beta$  neurodegeneration (Herrera et al., 2011a; Thinnes, 2013). This hormonal mechanism takes place through activation of Src-kinase and protein kinase A (PKA) signaling pathways (Herrera et al., 2011b). However, other kinases such as c-Jun N-terminal kinase-3 (JNK3) have been shown to regulate mitochondrial VDAC phosphorylation in the brain, thereby affecting the channel conductance and opening probability (Gupta, 2017). Overall, these data indicate that E2 modulation of VDAC phosphorylation in neuronal lipid rafts may be physiologically relevant in brain preservation. In support of this, a significant VDAC dephosphorylation has been observed in lipid rafts from cortical brain areas of menopausal women, in correlation with E2 detriment occurring during this period of women's life. Thus, in lipid rafts isolated from frontal cortex of women above 65 years old, post-transcriptional VDAC pattern was resolved in two main isoforms corresponding to non-phosphorylated forms as compared to samples from women younger than 55 years old (Canerina-Amaro et al., 2017). Similar results were obtained in AD samples from women at late stages of the disease, detecting a displacement to non-raft fractions of VDAC in parallel with dephosphorylation of the porine. The trafficking of VDAC out of lipid raft microdomains was accompanied by an impairment of ER-related signaling complex. These phenomena may have important consequences for cell preservation, as

E2 phosphorylation of VDAC in lipid rafts is an important prerequisite to palliate A $\beta$ -induced neurotoxicity (Herrera et al., 2011a; Fernandez-Echevarria et al., 2014). Indeed, selective estrogen receptor modulators (SERMs) such as tamoxifen show the opposite effects than the hormone, thus enhancing VDAC dephosphorylation (Herrera et al., 2011b) and gating (Valverde et al., 2002). Overall, although still inconclusive, these data indicate that hormone alterations in cortical post-menopausal lipid rafts may contribute to a progressive deterioration of neuronal functionality and survival through deregulation of VDAC.

Moreover, emerging evidence indicates a potential role of E2 in the lipid homeostatic preservation of the neuronal membrane, which is crucial to maintain stability of functional signalosomes.

## LIPID RAFT ALTERATIONS IN NEURODEGENERATIVE DISEASES

The brain is highly enriched in functional lipids and, consequently, the lipid homeostasis is particularly important in this organ. Given that lipid raft structure and activity require a particular proportion of distinct lipid classes, it follows that alterations in the lipid content in these microdomains can lead to abnormal functioning that may contribute to neuropathological events. Some results have reported that loss of lipid raft integrity correlates in general with brain aging progression. Different events may induce lipid impairment in these membrane structures, such as detriment in the lipid amount (either by intake or local bioynthesis), alterations in the proportion of polyunsaturated fatty acids (PUFA), increase in saturate/unsaturated ratio, and decrease in ganglioside or cholesterol levels that induce cell aging and death (Ledesma et al., 2012; Colin et al., 2016). It has been postulated that raft changes in lipid profile may induce modifications in the biophysical properties of these microstructures (e.g., peroxidability, viscosity, thermodynamics) that may contribute to neuronal detriment in cognitive brain areas (Diaz et al., 2015). Thus, in mice brains, subtle changes in the molecular composition of lipid rafts undergo an "aging" process throughout normal life that produces, among other events, an increase in membrane-order and reduction in the peroxidability index, notably impacting the lateral organization of these microstructures (Diaz et al., 2012). Indeed, these aberrant features are aggravated by AD-like genotype, observing an acceleration of lipid raft aging in parallel with AD progression (Fabelo et al., 2012b). Furthermore, alterations of lipid raft lipid matrix have been observed in age-associated neuropathologies even at pre-symptomatic stages, such as AD, PD, and dementia of Lewy bodies (DLB), suggesting that lipid raft impairment may be an early parameter of neuropathology (Fabelo et al., 2011, 2014; Marin et al., 2017). These changes are summarized in **Table 1**. Related to these dementias, the most significant lipid variations are the reduced levels of cholesterol, gangliosides, PUFA, plasmalogens, cerebroside, and sulfatides as compared with age-matched controls (Molander-Melin et al., 2005; Han, 2007; Fabelo et al., 2011; Ariga, 2017; Marin et al., 2017). Anomalies in

**TABLE 1** | Lipid alterations in neuronal lipid raft microdomains.

Lipid alteration	Neuronal tissue	Related anomalies and injury	References
- Reduced levels of PUFA (DHA, AA), and oleic acid	Frontal cortex	Alzheimer's disease at late stages (ADV-VI)	Martin et al., 2010
- Increased levels of the proportion of saturated fatty acids vs. PUFA			
- Reduced levels of PUFA (DHA, AA), oleic acid, and cerebrosides	Frontal cortex	Low levels of estrogen in menopause Alzheimer's disease at late stages (ADV-VI)	Canerina-Amaro et al., 2017
- Decreased levels of cholesterol and sphingomyelin			
- Lower levels of cholesterol, sterol esters, sulfatides, and PUFA (DHA, AA)	Neocortex	Double-transgenic APP/presenilin mice	Fabelo et al., 2012a
- Increased levels of sphingomyelin and saturated fatty acid content, and increased phospholipids/cholesterol ratio			
- The changes were highly significant in aged (14 months old) mice			
- Higher concentrations of gangliosides GM1 and GM2	Temporal cortex	Early and late stages of Alzheimer's disease	Molander-Melin et al., 2005
- Lower concentrations of cholesterol			
- Alterations in the levels of gangliosides	Frontal cortex Temporal cortex Parietal cortex Hippocampus Basal telencephalon	Alzheimer's disease and its mice models	Reviewed in Ariga (2017)
- Increased levels of GM1, GM2, GM3, GM4, GD3			
- Reduced levels of GD1b and GT1b			
- Lower levels of ganglioside GM1	Cortical areas	Parkinson disease	Di Pasquale et al., 2010
- Higher levels of ganglioside GM3			
- Reduced levels of cholesterol, gangliosides, PUFA (DHA, AA), plasmalogens, cerebrosides and sulfatides	Frontal cortex	Incidental Parkinson disease Parkinson disease	Fabelo et al., 2011
- Higher levels of saturated fatty acids (16:0 and 18:0)			
- Low levels of PUFA (DHA), plasmalogens and cholesterol	Frontal cortex	Dementia with Lewy bodies	Marin et al., 2017
- Alterations in ganglioside profiles	Human caudate region	Huntington's disease	Desplats et al., 2007
- Decreased levels of ganglioside GM1	Forebrain of R6/1 transgenic mice		
- Increased levels of GD3			
- Increased levels of glucosylceramide, hexosylsphingosine, bis(monoacylglycerol)phosphate and gangliosides	Occipital cortex from sheep	Neuronopathic Gaucher disease	Hein et al., 2017
- Decreased levels of cholesterol and phosphatidylcholine			
- Altered sphingolipid/cholesterol proportion			

lipid metabolism of lipid rafts have also been reported in other neurological diseases, such as Huntington's disease, where a marked reduction of ganglioside levels is observed in striatum and caudate regions which has been related to neuronal apoptosis (Desplats et al., 2007; Valencia et al., 2010). These observations suggest that targeted lipid variations in lipid raft normal molecular composition may be early events to progressive neuronal degeneration. Consequently, identification of these molecular alterations in cell membranes may predict future pathological outcome (Marin et al., 2013a).

A consequence of lipid instability of membrane microdomains is the alteration in the functionality, molecular interactions and trafficking of proteins integrated in signalosomes. Firstly,

the increased in viscosity and membrane order of these microstructures may reduce the lateral mobility and phase transition, thereby affecting lipid and protein interactions (Molander-Melin et al., 2005; Diaz et al., 2015). Secondly, proteins can be misfolded and adopt abnormal configurations that may lead to toxic aggregates and dysfunctional intracellular signaling. Thus, mounting evidence suggests that the key self-aggregating proteins in different proteinopathies, such as A $\beta$  in AD, alpha-synuclein ( $\alpha$ -syn) in PD, and prion protein (PrPc) in prion diseases share similar biophysical properties that may affect their biochemical interrelations with membrane-integrated molecular compounds (Goedert, 2015; Ugalde et al., 2016). Noticeably, lipid rafts are considered key sites in the modulation

of amyloid-like seeding (Kazlauskaitė et al., 2003; Arbor et al., 2016),  $\alpha$ -syn pathological fibrillation (Ariga, 2014), and the conversion of PrP<sup>c</sup> to the scrapie form PrP<sup>Sc</sup> (Taylor and Hooper, 2006). Thirdly, lipid rafts may act as membrane molecular sorting sites that coordinate the spatiotemporal rearrangement of signalosomes according to extracellular ligands availability (Simons and Gerl, 2010). As an example, changes in membrane cholesterol levels, that affect raft microstructure, can result in the stimulation of apoptotic events through activation or deactivation of different raft protein markers, such as receptors and channels (George and Wu, 2012). Taking into account the high number of signaling proteins intrinsically present in lipid rafts, it is conceivable that the consequences of abnormal lipid homeostasis may affect crucial functions such as synapsis, neuroplasticity, and cell preservation (Paratcha and Ibáñez, 2002; Tsui-Pierchala et al., 2002; Sebastião et al., 2013; Egawa et al., 2016). Fourthly, changes in lipid raft microenvironment may alter protein translocation to lipid rafts, thereby modifying their properties. According to this premise, some data support the concept that changes in lipid homeostasis and protein trafficking may underpin the etiology of AD. Notably, the regulation of electrogenic molecules involves their translocation to lipid rafts (Pristerá and Okuse, 2012). Also, accumulation and interaction of the key proteins involved in A $\beta$  processing, the amyloid precursor protein (APP) and  $\beta$ -secretase (BACE) is promoted by lipid alterations in raft microdomains (Parsons and Austen, 2007; Vetrivel et al., 2009). Additionally, this mechanistic pathological processing is initiated in cortical brain areas since the first AD stages (ADI-II) before senile plaques are evidenced, as a prelude to the typical anatomopathological events of this dementia (Fabelo et al., 2014). Moreover, although still not fully clarified, changes in raft lipid content observed in incidental PD and other synucleopathies may promote  $\alpha$ -syn toxic structural conformations (Samuel et al., 2016; Marin et al., 2017).

In correlation with this evidence, it is plausible that ER actions integrated in lipid raft platforms may be affected by variations in membrane lipid microenvironment that may ultimately alter estrogen signaling and cell responses (Marin, 2011). In agreement with this, lipid raft molecular analysis in cortical areas of post-menopausal women have shown some changes in the levels of cholesterol, cerebrosides, sterol esters, and PUFA as compared to younger women controls (Canerina-Amaro et al., 2017). Interestingly, a similar trend was reported in cortical lipid rafts from women with AD, detecting an exacerbation of normal lipid composition in these microdomains (Martín et al., 2010). Indeed, the biochemical structure of lipid rafts in cortical areas appears to be sufficient to discriminate between pre- and post-menopausal women, observing in the latter group closer similarities to lipid profiles than those characterized in lipid rafts from AD brains. Furthermore, these changes are known to affect the physico-chemical properties of lipid rafts that may subsequently alter the proteins integrated in these domains. In this order of ideas, ER $\alpha$ -related signalosome was altered in post-menopausal brains, observing a displacement out of the raft of, both, ER $\alpha$  and IGF-1R $\beta$  as a consequence of caveolin-1 dissociation (Marin et al., 2008; Canerina-Amaro et al., 2017). Taking into consideration the requirement of caveolin-1 to initiate E2 signal transduction

at the membrane level (Boulware et al., 2007; Luoma et al., 2008), these data suggest that ER-signalosome disruption may affect neuroprotective intracellular responses. In this sense, ER $\alpha$ /IGF-1R $\beta$ /caveolin-1 disarrangement also enhanced the redistribution of VDAC to non-raft fractions, in parallel with a dephosphorylation of the channel, which may increase neuronal vulnerability (Canerina-Amaro et al., 2017). Interestingly, ER $\alpha$ -signalosome disarrangements are exacerbated in cortical and hippocampal lipid rafts of AD brains (Ramirez et al., 2009), thereby supporting the relationship between membrane ER $\alpha$ -complex modifications and the process of aging and cognitive decline.

Overall, anomalies in lipid raft matrix appear to be an early event in neurodegenerative processes by modifying membrane protein clustering that regulates intracellular physiological responses. Consequently, preservation of membrane lipid homeostasis may be a key factor for preventing or decelerating neuronal dysfunction. In this sense, an emerging role of E2 has been associated with brain lipid balance (Pellegrini et al., 2014). These aspects are discussed in the next section.

## ESTROGEN AS LIPOSTATIC AGENT IN NEURONAL MEMBRANES

Emerging data suggest that E2 may play a role in lipid homeostatic balance of lipid rafts (Marin et al., 2013b; Maselli et al., 2015). These actions may take place through cross-talk interactions between the hormone and distinct lipid classes that play an important role in these microstructures' dynamics, such as PUFA and cholesterol. In this sense, based in nutrigenomic approaches, cholesterol and PUFA diets affect the expression of several genes involved in lipid raft formation (Puskas and Kitajka, 2006). Although still little explored, these estrogenic activities at the cell membrane may be highly relevant regarding E2-related activities for brain preservation.

The docosahexaenoic acid (DHA) is a PUFA highly abundant in the human brain (25–30% of total fatty acids), where it is a major component of cell membrane phospholipids. Paradoxically, the brain has very poor capacity to produce DHA (Pawlosky et al., 2001; Barceló-Coblijn and Murphy, 2009), which is a main limiting factor to ensure an adequate supply of this fatty acid to the nervous system. DHA plays a crucial role in proper brain development and function (Calder, 2017). It has been reported that a deficit of this PUFA increases the risk of cognitive impairment and dementia, in particular, AD and PD (Söderberg et al., 1991; Bazan et al., 2011; Salem et al., 2015; Colin et al., 2016; Sun et al., 2017). Brain beneficial actions of DHA take place at different levels, including: (i) Variations in membrane fluidity, permeability and elasticity due to its unsaturated conformation (Rawicz et al., 2000; Stillwell and Wassall, 2003); (ii) Involvement in intracellular signaling and apoptosis, and generation of neuroprotectins (Bazan, 2003, 2006); (iii) Modulation of membrane protein functioning (Calder, 2016); (iv) Regulation of the antioxidant system factors (Casañas-Sánchez et al., 2014, 2015). In particular, DHA appears to confer resilience against AD development rather



than a general effect throughout the brain, a phenomenon that may be related to the higher DHA turnover in regions involved in synaptogenesis and synapsis plasticity in learning and memory activities (Denis et al., 2013; Yassine et al., 2016). Moreover, although not particularly abundant in lipid rafts, DHA has a significant impact in the structure of these microdomains, due in part to the effects of this PUFA on cholesterol distribution (Wassall and Stillwell, 2009). In this order of ideas, reduction of DHA content in parallel with structural modifications of lipid rafts have been reported in different dementias, such as AD, PD, and DLB (Fabelo et al., 2011, 2014; Marin et al., 2017). DHA detriment occurring with aging may be partially explained by dietary deficits that may progressively affect the incorporation of this essential fatty acid into the membrane phospholipids, which are mainly replaced by monounsaturated fatty acids (Fabelo et al., 2012b, 2014). Thus, DHA supplementation has been associated with lower cerebral amyloidosis, higher cognitive, and memory performance, emotional disturbances, and cerebral vasculature improving during brain aging (Yurko-Mauro et al., 2010; Vellas et al., 2014; Boespflug et al., 2016).

An additional important factor in DHA turnover is associated with E2 regulation at the brain level. It is worth mentioning that, in addition to gonadal production, there is a local production of estrogens in the hippocampus (Galea et al., 2006; Hojo et al., 2008; Barker and Galea, 2009) although, at present, no clear demonstrations have shown a reduction of endogenous neurosteroids related to aging (Overk et al., 2013). Therefore, it is plausible that estrogen effects in DHA homeostasis may be the result of, both, local and peripheral estrogen origins. In this sense, it has been demonstrated that DHA plasma levels are about 15% higher in women than in men following similar control diets. Administration of oral ethinyl estradiol in women increased DHA by 42%. On the contrary, testosterone administrated to female-to-male transsexual subjects provoked a significant decrease (by 22%) in DHA concentrations (Giltay et al., 2004). These data indicate that E2, but not testosterone may enhance the synthesis of DHA from the diet precursor  $\alpha$ -linolenic acid (ALA). This biosynthesis takes place predominantly in the liver, which counts on the expression of the different elongases and desaturases needed to produce this PUFA (Cho et al., 1999). Thus, these data indicate that the greater capacity of women to convert ALA to DHA than do men (Burdge and Wootton, 2003) is related to E2 hormone. This E2 enhancer effect in DHA production may have important consequences on homeostasis of this fatty acid in the brain. Notably, despite the high abundance of DHA in the brain, this organ has a very low capacity to endogenous synthesis of this fatty acid (Plourde and Cunnane, 2007; Brenna et al., 2009). Yet it is generally accepted that neuron and glial cells possess the genetic machinery to synthesize *de novo* saturated and monosaturated fatty acids, and nerve cells are also endowed with the enzymes to produce PUFA (Bazinet and Layé, 2014). However, PUFA content in the brain is mainly provided by the blood, and the rate of PUFA uptake into the nervous system is much higher than the local production. Thus, *in vivo* studies in humans have demonstrated that only a 0.5% of ALA is converted to DHA (Plourde and Cunnane, 2007). Moreover, even though PUFA dietary supply appears to upregulate the

expression of the enzymes involved in DHA synthesis in the liver, in contrast, enzyme levels remain static in the brain (Rapoport, 2013). In agreement with this, it has been recently reported that dietary DHA supplementation in mice does not significantly increase the local expression of the elongases and desaturates involved in DHA synthesis in the hippocampus (Díaz et al., 2016). Collectively, these results indicate that DHA content in the brain depends on a constant supply from the peripheral blood.

Based upon these observations, it is plausible that the combinatory effects of E2 and DHA factors may have significant consequences in nerve cell biology and brain preservation. Likely, the best characterized evidence of the DHA and E2 interplay in humans is the demonstration of a higher prevalence rate of depression following DHA deficiency and ovarian hormonal dysregulation (Davis et al., 2010). Indeed, it has been reported a synergistic antidepressant action of DHA and E2 in the regulation of serotonergic neurotransmission through brain-derived neurotrophic factor (BDNF) and inflammatory cytokines (Jin and Park, 2015). These antidepressant-like effects were specific of DHA since its precursor alpha-linolenic acid did not show any effect in serotonergic circuits (Choi and Park, 2017).

Moreover, the combination of DHA-enriched diets and E2 treatment appears to be a key factor in maintaining lipid homeostasis in the hippocampus (Díaz et al., 2016). These E2-related lipostatic mechanisms involve the genetic regulation of lipid biosynthetic pathways, which are crucial for hippocampal maintenance against AD phenotype in mice, in particular, at early stages of this pathology (Marin et al., 2013b; Díaz et al., 2016). Other evidence of the importance of E2 in DHA bioavailability in the brain has been reported during pregnancy, where there is a preferential high demand of DHA for the fetal brain formation. In this instance, it has been demonstrated that E2 is the main factor of brain DHA uptake in both the maternal and fetal brain, with a higher production of PUFA in the maternal liver also observed (Fabelo et al., 2012a). These data suggest that the hormone may play a role in, both, brain intake and brain production of DHA. Other experiments in cultured cells support the idea that E2 upregulates the metabolic production of DHA from its precursors. Thus, *in vitro* experiments in human neuroblastoma SHSY-5Y cells have reported that these cells maintain the ability to convert a certain proportion of ALA to DHA. Interestingly, E2, but not dehydroepiandrosterone, upregulates the DHA production (by 50%), and its uptake into the plasma membrane (Alessandri et al., 2008). This E2 mechanism involves the modulation of the Delta5-desaturase expression (Extier et al., 2009). These observations suggest that E2 may be an enhancer of the neuronal endogenous production of this PUFA, and may satisfy to a certain degree meet the neuronal membrane demands of DHA. However, the highest proportion of DHA present in neuronal membranes comes from diet sources. Furthermore, E2 and DHA modulation in the brain may be dual, since dietary DHA intake conversely potentiates E2 synthesis in the cerebral cortex, a factor that is required to delay the onset and elongate the latency of epileptic seizures (Ishihara et al., 2017). Overall, these studies reveal the synergistic efficacy of E2 and DHA in physiological actions in the brain.

A big body of data has reported the role of membrane cholesterol in the neuroprotective effects of E2 (Peri et al., 2011). The brain contains about 25% of the total amount of unesterified cholesterol content in the total body. Therefore, it is plausible that cholesterol embedded into the neuronal membranes, and not just its peripheral levels, may be a key factor for brain maintenance and functionality (Yanagisawa, 2002). In this scenario, it has been reported that cholesterol plays a multifactorial role in cell membranes. Thus, this molecule is a key factor for lipid rafts microstructure and functionality (Egawa et al., 2016), and its optimal amount may create a protected barrier against toxic factors (Arispe and Doh, 2002). Some studies also reported that raft cholesterol may have a role in the biogenesis and catabolism of  $\beta$ -amyloid (Araki and Tamaoka, 2015). In particular in lipid rafts,  $\beta$ -amyloid formation may be influenced by cholesterol turnover that affects the fluidity and structural properties of these microdomains. Thus, a loss of neuronal membrane cholesterol facilitates  $\beta$ -amyloid formation machinery (Abad-Rodriguez et al., 2004). In accordance with this, low cholesterol levels have been detected in cortical lipid rafts from AD patients in parallel with increased levels of steryl/cholesteryl esters (Martín et al., 2010).

Estrogens may play a preferential role for the control of cholesterol synthesis and trafficking in the neuronal membranes. Recent findings have indicated that the production of this fatty acid is stimulated by estrogens. Some data has reported that E2 affects cholesterol synthesis in the hippocampus, through the modulation in expression of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoAR) and acetyl-coenzyme A acetyltransferase (ACAT) genes (Marin et al., 2013b; Díaz et al., 2016). This action may be achieved by the intervention of seladin-1 (for SElective Alzheimer's Disease INDicator-1), a molecule that plays a dual role as a neuroprotector agent as well as a catalyzer of cholesterol formation from its precursor desmosterol (Peri, 2016).

Another important level of interaction of E2 and lipid transport in the brain takes place through the expression of apolipoprotein ApoE. This lipoprotein is a crucial regulator of cholesterol metabolism in the brain. Different ApoE forms (ApoE2, ApoE3, and ApoE4) have been characterized. In this sense, ApoE4 is the greatest genetic risk factor to develop sporadic AD, and this risk is greater in women than men (Neu et al., 2017). In particular, (Apo)E3 isoform is stimulated by this hormone, to facilitate neurite outgrowth (Nathan et al., 2004). Distinct regulation of ApoE isoforms by estrogens may have an important role in neuroprotection against AD, since hormonal administration at menopause have benefits in ApoE2 and ApoE3 production in women by decreasing extracellular and soluble  $\beta$ -amyloid (Kunzler et al., 2014). These observations suggest a distinct E2 modulation of Apo subtypes, which may have important consequences in neuroprotection against AD (Shi et al., 2014).

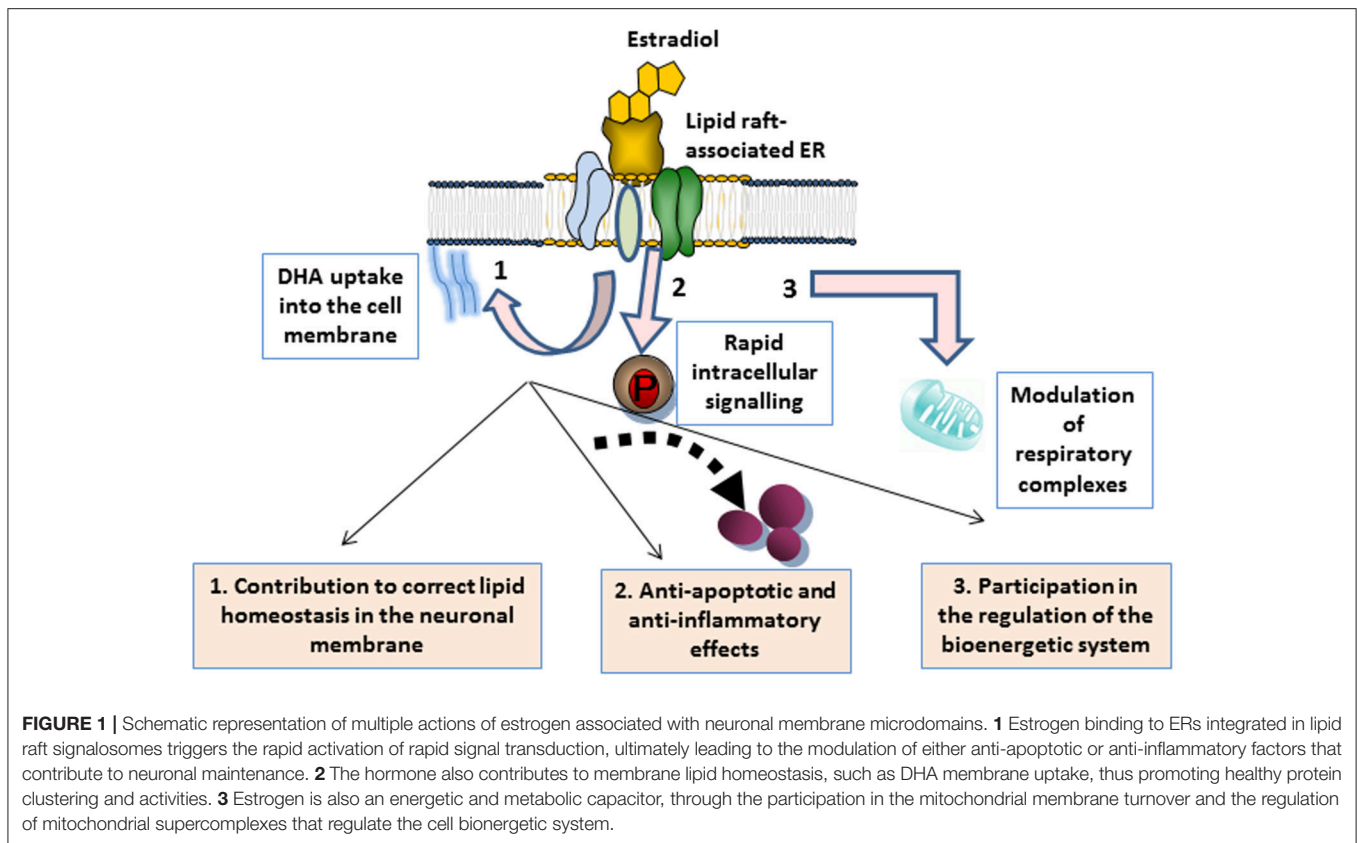
Overall, these data reflect the importance of E2 in lipid synthesis and uptake in the brain throughout women's lifespan that can be affected as a consequence of hormonal changes.

## FUTURE PERSPECTIVES

As discussed throughout the different sections, a growing body of evidence supports that E2 has a beneficial impact in the brain by exerting multiple actions that work in conjunction with neuronal membrane microenvironments. These actions are summarized in **Figure 1**. In plasma membrane lipid rafts, E2 plays a dual action. On the one hand, it targets ER $\alpha$  clustered in multimeric signalosomes formed by different molecules that trigger neuroprotective signal transduction. On the other hand, it contributes to the maintenance of the proper lipid environment to promote healthy molecular interactions for neuronal functioning. In particular, evidence indicates that E2 modulates cell membrane intake of cholesterol and DHA abundantly represented in the nervous system, and significantly contribute to lipid raft structure (Su, 2010; Peri et al., 2011; Marin et al., 2013b). Preservation of lipid homeostasis in these microdomains appear to be crucial for protein stability and interactions in signaling platforms, but it may also contribute to enhance neuronal defenses against oxidative stress (Casañas-Sánchez et al., 2014). It is worth mentioning that, although still not fully demonstrated, steroid hormone contribution to membrane molecular turnover may also take place at the mitochondrial membrane level. Thus, lipid rafts have also been identified in mitochondria, where they have important implications in optimal assemblies of respiratory supercomplexes and apoptosis regulation (Garofalo et al., 2015). In these organelles, lipid rafts may participate in energetic and metabolic capacity (Ray et al., 2016). Moreover, some reports have indicated that particular lipid features of lipid rafts may promote specific protein assemblies for mitochondrial functioning. In this order of ideas, it has been demonstrated that DHA content modulates the molecular architecture of cardiolipin-protein scaffolds, which are the pivotal structure of mitochondrial lipid rafts (Shaikh et al., 2015). Therefore, it is conceivable that lipid anomalies in lipid rafts induced by estrogenic fluctuations may converge in reduced energy production and cell exhaustion (Ferrer, 2009). However, this possibility remains to be confirmed.

Given that E2 detriment occurring during menopause enhances the risk of neuropathological events, estrogen replacement therapy (ERT) may be considered a logical intervention. Nevertheless, ERT approaches are still a matter of controversy, because of the increased rates of stroke, coronary heart disease, and breast cancer reported in menopausal women following this preventive therapy (Prentice, 2014). A major reason for these unsuccessful trials is lack of standard criteria and optimization of the parameters for accurate hormonal treatments. For instance, there remains much to be learned concerning the optimal treatment guidelines regarding formulation, dose and timing of intervention to avoid unfavorable health consequences (Manson et al., 2013). However, taking into account the potential benefits of this type of therapies in nervous system preservation, further research to determine the best ERT strategy is crucial, although remains still pending.

Some promising data accrued from human studies have provided evidence that estrogen replacement therapies (ERT) administrated to women at 50–63 years old might protect against



cognitive decline occurring during normal aging (Henderson, 2014). Thus, it has been demonstrated that ERT improves performance on tests of verbal, visual working and spatial memory, and verbal fluency, as compared to non-users women of similar age (Robinson et al., 1994; Kimura, 1995; Grodstein et al., 2000; Miller et al., 2002; Sherwin and Henry, 2008). However, there are multiple factors such as the particular physiological features of each subject (age, health, hormone status, etc.) that make ERT unsuitable for some women in long-term basis (Marjoribanks et al., 2017). In addition, there is not still consensus about the efficacy of hormone treatments in the brain due to multifactorial parameters, including E2 origin, dose, and timing of duration that may largely influence either efficiency or adverse risk factors (Hogervorst et al., 2000). In this sense, a proposed alternative strategy is the development of efficacious NeuroSERM (specific SERMs designed for the brain) that may avoid the peripheral adverse effects in other E2-targeted organs (Zhao et al., 2005). However, this endeavor requires a better knowledge of the orchestrated estrogen mechanisms of action at the different subcellular compartments in nerve cells.

An alternative intervention that appears to alleviate the impact of metabolic changes during menopausal periods is based on nutritional supplementation with vegetable phytoestrogens (Villa et al., 2017). Phytoestrogens have similar structures to those of estrogen, possess estrogen-like activities, and show some affinity for ERs (Brzezinski and Debi, 1999). Consequently, supplementation with the most common phytoestrogens, such

as isoflavones (i.e., genistein), and stilbenes (i.e., resveratrol) is a remedy used for a significant number of women to alleviate some menopausal symptoms (Soni et al., 2014). Isoflavones are abundant in soybean products (e.g., tofu), and resveratrol is highly abundant in grape skin and berries. Interestingly, some evidence indicates that supplementation with either isoflavones or resveratrol to menopausal women in early stages (<10 years) show some beneficial effects in memory and cognition, as well as improved cerebral vascularization (Evans et al., 2016; Thaug Zaw et al., 2017).

Furthermore, emerging data discussed in this review have demonstrated a synergistic effect of, both, E2 and essential fatty acids such as DHA in the maintenance of neural homeostasis and preservation against neurodegeneration (Fabelo et al., 2012a; Díaz et al., 2016). Based on these premises, future potential interventions may include supplementation of, both, hormonal treatments and selected lipid classes that may have beneficial effects during menopausal periods. In particular, specific nutritional supplements enriched in omega-3 fatty acids abundantly found in fish oil (i.e., DHA) combined with phytoestrogens may provide protection against cognitive aging. In this sense, some promising studies in cancer cellular models have indicated that diets rich in fish oils and soy isoflavones may be a good complementary treatment against breast cancer (Duncan et al., 2005), and osteoporosis (Kruger et al., 2015). Indeed, the combination of these two compounds appear to reduce breast cancer risk by enhancing anti-inflammatory

pathways and lowering the pro-inflammatory effects induced by prostanoids, cyclooxygenase-2 (COX-2), and arachidonic acid (AA) activities (Horia and Watkins, 2007). In agreement with this, other data have also shown that reduced levels of DHA as a consequence of diets poor in this PUFA promote inflammation in distinct neuropathologies (Sinclair et al., 2007; Zárate et al., 2017). Moreover, the fact that studies in experimental mouse models of AD have demonstrated a deleterious effect in the hippocampus of low levels of, both, E2 and DHA, also supports the existence of a PUFA/hormone synergistic neuroprotective effect (McNamara et al., 2009). However, to the best of our knowledge, no studies have addressed the potential beneficial effects of dual supplementary intake of PUFA and phytoestrogen in human nervous system.

In conclusion, we believe that nutritional-hormonal interventions may be a potential therapeutic strategy to alleviate some of the symptoms associated with, both, menopause and age-related brain degeneration, particularly at the stage of

earliest recognizable symptoms. These strategies may act as compensatory mechanisms to palliate the loss of essential cell membrane lipids that ultimately may lead to neuronal dysfunction and brain detriment. Notwithstanding these encouraging results, further studies will be needed to tackle optimal strategies to mitigate menopausal effects in the nervous system.

## AUTHOR CONTRIBUTIONS

RM is the main contributor to this work; RM and MD have written the main body of the text, and provided the content of the different sections of this review.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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