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Neuroprotective actions of selective estrogen receptor modulators

Lydia L. DonCarlos¹, Iñigo Azcoitia², and Luis M. Garcia-Segura³

¹ Department of Cell Biology, Neurobiology and Anatomy, Stritch School of Medicine, Loyola University Chicago, 2160 South First Avenue, Maywood, Illinois 60153, USA. Tel: +1-7082164975; Fax: +1-7082163913; e-mail: ldoncar@lumc.edu

² Departamento de Biología Celular, Facultad de Biología, Universidad Complutense, E-28040 Madrid, Spain. Tel: +34-913944861, Fax: +34-913944981 e-mail: azcoitia@bio.ucm.es

³ Instituto Cajal, CSIC, E-28002 Madrid, Spain. Tel:+34-915854729; Fax: +34-915854754; e-mail: limgs@cajal.csic.es

Summary

Decreasing levels of sex hormones with aging may have a negative impact on brain function, since this decrease is associated with the progression of neurodegenerative disorders, increased depressive symptoms and other psychological disturbances. Extensive evidence from animal studies indicates that sex steroids, in particular estradiol, are neuroprotective. However, the potential benefits of estradiol therapy for the brain are counterbalanced by negative, life-threatening risks in the periphery. A potential therapeutic alternative to promote neuroprotection is the use of selective estrogen receptor modulators (SERMs), which may be designed to act with tissue selectivity as estrogen receptor agonists in the brain and not in other organs. Currently available SERMs act not only with tissue selectivity, but also with cellular selectivity within the brain and differentially modulate the activation of microglia, astroglia and neurons. Finally, SERMs may promote the interaction of estrogen receptors with the neuroprotective signaling of growth factors, such as the phosphatidylinositol 3-kinase/glycogen synthase kinase 3 pathway.

Keywords

Estrogen receptors; Gliosis; Glycogen synthase kinase 3; Growth factors; Selective estrogen receptor modulators

Neurological effects of estrogens

The ovarian hormone 17 β -estradiol acts in the central nervous system to regulate neuroendocrine events and reproduction. Estradiol regulates gene expression, neuronal survival, neuronal and glial differentiation, and synaptic transmission and has anti-inflammatory, protective and reparative properties in the brain (Garcia-Segura and Melcangi, 2006; Woolley, 2007; Spencer et al., 2008; Vegeto et al., 2008). Endogenous sex hormone levels play an important role in maintaining cognitive function in the elderly (Yaffe et al., 2007) and most studies suggest that estrogen therapy increases memory and cognitive function

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in healthy women (Yaffe et al., 1998; Henderson et al., 2000; Resnick and Maki, 2001; Krug et al., 2006; Sherwin, 2006). Estrogen therapy is also associated with an increase in the volume of the hippocampus (Lord et al., 2008), a brain region involved in cognitive function and spatial memory. In addition, 17 β -estradiol prevents cognitive and neuronal loss in many experimental animal models of neurodegeneration (Garcia-Segura et al., 2001; Suzuki et al., 2006; Simpkins and Singh, 2008). For example, 17 β -estradiol reduces neurodegenerative damage (Wise, 2003a) and promotes neurogenesis in the subventricular zone (Suzuki et al., 2007b) after middle cerebral artery occlusion in mice. 17 β -Estradiol is also protective in animal models of Parkinson's (Morissette et al., 2008a) and Alzheimer's diseases (Carroll and Pike, 2008). However, there has not been an unambiguous translation of the data from animal models to human studies on the possible protective effects of therapy with estrogens and progestins, or estrogen-only, on neurological and cognitive function in postmenopausal women. Thus, although some studies have reported that estrogen therapy may reduce the motor disability associated with Parkinson's disease, decrease the risk of stroke in postmenopausal women, prevent or delay the onset of Alzheimer's disease and improve cognition for women with Alzheimer's disease, other studies have not detected these positive effects, and in some cases, have identified possible negative effects of hormone therapy (Shaywitz and Shaywitz, 2000; Viscoli et al., 2001; Saunders-Pullman, 2003; Wise, 2003b; Ragonese et al., 2006; Resnick et al., 2006; Maki et al., 2007; Henderson, 2008; Vegeto et al., 2008). For example, results from the Women's Health Initiative (WHI) randomized trial, in which participants received 1 daily tablet of 0.625 mg of conjugated equine estrogens plus 2.5 mg of the synthetic progestin, medroxyprogesterone acetate, or a matching placebo, suggested an increased risk of dementia and stroke as a result of long-lasting hormone treatment initiated several years after menopause (Shumaker et al., 2003; Wassertheil-Smoller et al., 2003; Yaffe, 2003).

Several possible explanations have been proposed for the discrepant results among different studies, including differences in dose, route of administration, specific hormone formulation, length of treatment, sample size, and age of the women receiving the treatment. For instance, different progestins may have very different effects on the brain. Natural progesterone, which can be transformed in neural tissues into the neuroprotective metabolites dihydroprogesterone and tetrahydroprogesterone, may have better protective effects than synthetic progestins (Nilsen and Brinton, 2002; Ciriza et al., 2006; Nilsen et al., 2006). However, the use of progestins in combination with estrogens cannot completely explain the lack of beneficial effects of hormone therapy on brain function, because not even the results from the estrogen-alone arm of the WHI study have supported the hypothesis that estrogens will have beneficial effects in women as expected based on animal studies (Espeland et al., 2004; Shumaker et al., 2004). In addition, it is important to emphasize that most basic animal studies on neuroprotective effects of estrogens are based on the use of 17 β -estradiol, not a mixture of estrogens as in the WHI study. The difference is relevant, since available evidence indicates that different natural estrogens have different outcomes for neuroprotection (Picazo et al., 2003; Zhao and Brinton, 2006).

Importantly, the WHI data are applicable to long-term hormone therapy started in women aged 65 or more years, whereas the risks and long-term benefits of either short-term or long-term hormone therapy begun in younger women are not yet well known. The focus of the WHI study on women who are already many years beyond the onset of menopause posed a serious limitation because, in the years after the WHI study was initiated, evidence emerged that the peri-menopause may be a critical period for the highest efficacy of hormone therapy in the prevention of brain disorders (Maki, 2006; Sherwin, 2007). Indeed, multiple epidemiological studies have shown that estrogen therapy at the time of menopause decreases the later risk of dementia, including Alzheimer's disease (LeBlanc et al., 2001) and a prospective study on postmenopausal women in Cache County, Utah, indicates that estrogen therapy at the time of menopause and continued for 10 years decreases the risk of Alzheimer's disease (Zandi et al.,

2002). However, the WHI trials were not performed in perimenopausal women, but rather were performed on older women; moreover, these women had no known risks for cognitive dysfunction. Little information is available on the reparative properties, as opposed to protective actions, of estrogens. The neuroprotective effects of estradiol in a healthy brain may contribute to maintaining normal brain function. However, regenerative actions in a damaged, as opposed to healthy, neuronal circuit might have a negative rather than positive impact on brain function (Zhao et al., 2005). Similarly, our knowledge of how estrogen receptors are regulated is deficient. In particular, it is important to explore how aging and either long-term hormone deprivation or long-term hormone replacement may affect responsiveness to 17 β -estradiol. Indeed, the results from experimental studies in animal models of stroke indicate that a prolonged period of estrogen deprivation disrupts both neuroprotective and antiinflammatory actions of 17 β -estradiol (Suzuki et al., 2007a). In any case, the conflicting results of the WHI study and other clinical trials, as well as the results of animal studies, emphasize the need for a better understanding of the effects of 17 β -estradiol and estrogens in the brain at multiple stages of the life-cycle.

The mechanisms involved in 17 β -estradiol action in the brain should be explored in more detail, but some possible alternatives for therapeutic intervention can be envisaged even as we continue to collect more information from basic science studies. Ideally, these alternatives should be free of the thrombotic and neoplastic risks associated with estrogen therapy. Several laboratories are exploring new alternatives for hormone therapy to prevent the neurodegeneration, cognitive decline and affective disorders that are associated with hormone changes with aging and menopause. Here, we will briefly review the use of neuroprotective estrogenic compounds, such as selective estrogen receptor modulators (SERMs) and non-feminizing estrogens, which do not have as many of the negative peripheral effects associated with estrogen therapy.

Neuroprotective actions of SERMs: molecular mechanisms

Estrogen receptors are candidate targets for neuroprotective therapies based on estrogen actions. SERMs, either synthetic or natural, such as phytoestrogens, may represent an alternative to estradiol for the treatment or the prevention of neurodegenerative disorders. Several studies have shown that some synthetic SERMs, such as tamoxifen, raloxifene or toremifene (Callier et al., 2001; Rossberg et al., 2000; Dhandapani and Brann, 2002; Kimelberg et al., 2003; Mehta et al., 2003; Ciriza et al., 2004; Mickley and Dluzen, 2004; Zhao et al., 2005; Kokiko et al., 2006; Zhao et al., 2006) and some natural SERMs, such as genistein (Azcoitia et al., 2006), are neuroprotective in vitro and in vivo. These findings open the door to the possibility that new SERMs might be developed that would lack feminizing effects and would preferentially target the nervous system (NeuroSERMs) to promote cognitive function and to reduce the risk of neurodegenerative diseases (Brinton, 2002, 2004; Zhao et al., 2005).

The neuroprotective actions of SERMs in the brain may be mediated by their binding to classical nuclear estrogen receptors (Fig. 1), which are ligand-dependent transcription factors (Nilsson et al., 2001) that belong to the steroid/thyroid nuclear receptor superfamily. When activated, estrogen receptors homo- or heterodimerize, interact with DNA and recruit a cohort of transcriptional cofactors to the regulatory regions of target genes. In addition, the activated estrogen receptors can interact with other transcription factors to stabilize binding of these transcription factors to specific response elements in the DNA and recruit specific coactivators or corepressors that ultimately activate transcriptional machinery (Klinge, 2000; McKenna and O'Malley, 2002; Belandia and Parker, 2003). SERMs interact with estrogen receptors and have tissue-specific effects distinct from those of estradiol, acting as estrogen receptor agonists in some tissues and as antagonists in others (Riggs and Hartmann, 2003; Smith and O'Malley, 2004). Therefore, some SERMs may have estrogenic actions in some brain regions but an

absence of estrogenic actions, or even anti-estrogenic effects, in other brain regions or peripheral tissues.

The two mammalian estrogen receptors cloned to date, α and β , are expressed in the brain. Estrogen receptor α is abundantly expressed in many brain areas, including the hippocampus, hypothalamic/preoptic continuum, amygdala, midbrain, dorsal horn of the spinal cord and dorsal root ganglia (Shughrue et al., 1997a). Estrogen receptor β is also expressed in these regions (Li et al., 1997; Shughrue et al., 1997a,b), and in other brain regions, such as the cerebellum, it is the predominant form of classical estrogen receptor (Shughrue et al., 1997a). In some regions, these two estrogen receptors are colocalized within the same cells, whereas in others, only one form is expressed in a given cell (Shughrue et al., 1998). Moreover, the role of each estrogen receptor in neuroprotection appears to be dependent on the cellular parameter analyzed, the type of injury as well as the location of injury (Merchenthaler et al., 2003; Cordey and Pike, 2005; Miller et al., 2005; Dubal et al., 2006; Brann et al., 2007; Suzuki et al., 2007b; Morissette et al., 2008b). Therefore, SERMs selective for each estrogen receptor subtype may provide an interesting therapeutic instrument to target specific neuroprotective mechanisms and specific brain pathologies (Carswell et al., 2004; Zhao et al., 2004; Cordey and Pike, 2005; D'Astous et al., 2006; Zhao and Brinton, 2007; Morissette et al., 2008b).

As in other organs, estradiol and SERMs may act in the brain through mechanisms other than the regulation of transcription by the activation of classical nuclear estrogen receptors (Fig. 1). Estrogenic compounds may also elicit rapid membrane and cytoplasmic actions by membrane-initiated steroid signaling (Kelly et al., 2005; Hammes and Levin, 2007; Kelly and Rønnekleiv, 2008; Vasudevan and Pfaff, 2008). Membrane-initiated steroid signaling may be mediated by putative non-nuclear estrogen receptors located in the cytoplasmic and membrane compartments of neurons and glial cells (Arvanitis et al., 2004; Milner et al., 2001, 2005; Pawlak et al., 2005; Gorosito et al., 2008; Kelly and Rønnekleiv, 2008; Marin et al., 2008; Micevych and Mermelstein, 2008; Hirahara et al., 2009). 17β -Estradiol and SERMs may also act in the nervous system through nonspecific receptors, such as neurotransmitter ion channels and through non-receptor-mediated mechanisms, for example, as an anti-oxidant (Behl, 2002). The actions of estrogenic compounds via the membrane, cytoplasmic and nuclear receptors are undoubtedly, in many cases, inextricably linked (Levin, 2005; Hammes and Levin, 2007; Kelly and Rønnekleiv, 2008; Vasudevan and Pfaff, 2008). The gene products generated by estrogen-dependent activation of nuclear receptors and transcription can be post-transcriptionally modified by cell signals activated by membrane estrogen receptors. Transcription itself can be augmented or reduced by co-activators and co-repressors previously modified through membrane-associated estrogen receptor actions. Estrogenic compounds not only drive the transcription of genes whose promoters bind nuclear estrogen receptors, but also of genes that are transactivated by other transcription factors modified after membrane estrogen signaling. An avenue for future research will be to understand better the coordinate regulation of cellular function through the intersection of non-nuclear and nuclear effects of estrogen receptor activation.

To date, many rapid actions of estrogens that are not dependent on transcriptional activation have been identified in the brain, but the molecular identity of non-classical estrogen receptors has not been fully characterized. The extranuclear functions of estrogenic compounds may be mediated in part by receptors identical to the classical nuclear estrogen receptors, but in some way modified (for instance, palmitoylated) in order to prevent, at least temporarily, their translocation to the nucleus. While the predominant localization of classical estrogen receptors is in the cell nucleus, ultrastructural analyses have demonstrated that estrogen receptor α and β immunoreactivity is also present in dendritic spines, axons, synapses and glial cell processes, in a position that could favor cytoplasmic signaling (Milner et al., 2001, 2005; Hart et al., 2007). In addition, estrogen receptors have been identified in the plasma membrane of neurons

and glial cells (Arvanitis et al., 2004; Pawlak et al., 2005; Gorosito et al., 2008; Kelly and Rønnekleiv, 2008; Marin et al., 2008; Micevych and Mermelstein, 2008; Hirahara et al., 2009).

Membrane associated estrogen receptors may be part of macromolecular entities aggregated in specific plasma membrane domains, the caveolae, where they can hypothetically interact with G-proteins, receptor tyrosine kinases, non-receptor kinases, and other signaling partners (Toran-Allerand, 2004; Luoma et al., 2008; Marin et al., 2008, 2009). Estrogen receptors can directly contact G-proteins or transactivate other G-protein coupled receptors, leading to the stimulation of ion channels and phospholipase C (Kelly et al., 2002). In addition, GPR30 is a seven transmembrane domain protein that has been identified as a putative membrane estrogen receptor (Hewitt et al., 2005; Revankar et al., 2005), binds natural estrogens, SERMs and phytoestrogens and is present in the plasma membrane of hippocampal neurons (Funakoshi et al., 2006). Inactivation of GPR30 eliminates the effects of 17 β -estradiol on neuroendocrine responses to serotonin receptor 1A agonists, whereas activation of GPR30 in the paraventricular nucleus modulates neuroendocrine responses to serotonin receptor 1A in a manner similar to 17 β -estradiol (Xu et al., 2009). However, experiments in mice that were double knockouts for estrogen receptors α and β failed to detect any membrane estrogen binding (Pedram et al., 2006), suggesting that membrane associated effects of 17 β -estradiol and SERMs are specific to these classical nuclear receptors acting in a nonclassical manner. Therefore, GPR30 may be relevant to 17 β -estradiol signaling but may require intact classical estrogen receptors to function, and can be kept in mind as a potential future target for neurotherapeutic approaches using estrogens.

The action of 17 β -estradiol and estrogenic compounds in the brain and the activity of estrogen receptors may differ depending on the availability of other factors that may be affected by aging, menopause or pathology. These include transcription factors, such as AP1 (Webb et al., 1995), NF-kappaB (Dodel et al., 1999) and STAT3 (Ciana et al., 2003; Gao et al., 2007) and growth factors, such as brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-I (IGF-I). The BDNF gene contains an estrogen response element in the promoter region and, thus, estrogens may directly modulate the transcription of this neurotrophin (Sohrabji et al., 1995). Furthermore, estrogen receptors and BDNF are coexpressed in several neuronal cell types (Sohrabji and Lewis, 2006). Estradiol-dependent upregulation of BDNF transcription is involved in the survival of cholinergic neurons projecting to the hippocampus and a rise in BDNF mRNA levels in the intact female rat has been correlated with better hippocampal function (Scharfman and Maclusky, 2005, 2006). In this scenario, 17 β -estradiol is an indispensable factor in many of the phenomena that elevate BDNF, such as physical exercise (Berchtold et al., 2001). Alterations in the interactions between 17 β -estradiol and BDNF in the brain may contribute to a variety of neurological and psychiatric disorders (Scharfman and Maclusky, 2005, 2006).

Estrogen receptors and IGF-I receptors cooperate in neuroprotection in animal models of hippocampal neurodegeneration, Parkinson's disease and global cerebral ischemia (Azcoitia et al., 1999; Quesada and Micevych, 2004; Garcia-Segura et al., 2006; Mendez et al., 2006; Jover-Mengual et al., 2007). When IGF-I receptor is inhibited by a specific antagonist, estradiol is unable to protect hippocampal or dopaminergic mesencephalic neurons from neurodegenerative damage (Azcoitia et al., 1999; Quesada and Micevych, 2004; Jover-Mengual et al., 2007). Conversely, IGF-I mediated neuroprotection is blocked by the antiestrogen ICI 182,780 (Azcoitia et al., 1999).

The mechanism of interaction of estrogens and growth factors may involve coordinate activation of signal transduction pathways. Indeed, BDNF, IGF-I and other trophic factors can activate extracellular-regulated kinases (ERKs), members of the family of mitogen-activated

protein kinases (MAPK), which may be involved in the neuroprotective effects of estrogenic compounds. The ability of estrogenic compounds or circulating 17 β -estradiol to activate members of the MAPK family, ERK1 and ERK2, has been demonstrated in neuroblastoma cells (Watters et al., 1997), cortical explant cultures (Singh et al., 2000), cultured primary neurons from different brain regions (Zhao et al., 2005) and in the hippocampus of the cycling female rat (Bryant et al., 2005). In addition, robust ERK1/2 activation is detected in the brain after 17 β -estradiol administration in vivo (Mendez et al., 2006). Estrogen activation of ERK1/2 may elicit mechanisms of neuroprotection, since treatment with MAPK inhibitors reduces the neuroprotective effects of estrogens (Jover-Mengual et al., 2007; Zhao and Brinton, 2007).

Estrogenic compounds may interact with the signaling pathways of growth factors by direct actions on classical estrogen receptors acting outside the nucleus. Thus, estrogen receptor α , in an estrogen dependent process, can physically interact with IGF-I receptor and with the downstream proteins insulin receptor substrate 1 (IRS-1) and PI3K, enhancing IGF-I signaling in the brain (Mendez et al., 2003, 2006; Marin et al., 2009). In addition, IGF-I receptor and estrogen receptor activation synergistically increase the activity of the kinase Akt (Cardona-Gomez et al., 2002), and coordinately regulate protection from neurotoxicity (Mendez et al., 2006). The neuroprotective actions of 17 β -estradiol and SERMs may be in part mediated by the activation of Akt, which is known to increase the expression of the anti-apoptotic protein, Bcl-2 (Cardona-Gomez et al., 2001; Nilsen and Brinton, 2003; Wise et al., 2005; D'Astous et al., 2006). In addition, downstream of Akt there is another important kinase involved in the regulation of neuronal survival: glycogen synthase kinase 3 β (GSK3 β). 17 β -Estradiol and some SERMs inhibit the activity of GSK3 β in the brain (Cardona-Gomez et al., 2004; Goodenough et al., 2005; D'Astous et al., 2006; Mendez et al., 2006). Increases in GSK3 β activation have been strongly associated with neurodegenerative disorders and stroke, and inhibition of GSK3 β activates surviving signaling pathways in neurons (Bhat et al., 2000, 2004; Enguita et al., 2005). Therefore GSK3 β , and 17 β -estradiol or SERM inhibition of GSK3 β activity, has emerged as an important therapeutic target. 17 β -Estradiol regulates the interaction of estrogen receptor α with GSK3 β and β -catenin, another molecule involved in the regulation of neuronal survival and in the reorganization of the cytoskeleton as well as synapse stabilization (Cardona-Gomez et al., 2004). Furthermore, 17 β -estradiol regulates the interaction of the microtubule-associated protein Tau, with GSK3 β , β -catenin and elements of the PI3K complex (Cardona-Gomez et al., 2004) and reduces the hyperphosphorylation of Tau (Cardona-Gomez et al., 2004; Alvarez-de-la-Rosa et al., 2005), one of the molecular markers of Alzheimer's disease. All of these actions may be involved in the plastic and neuroprotective effects of 17 β -estradiol and SERMs.

Another important mechanism involved in the neuroprotective effects of estrogenic compounds is the regulation of mitochondrial function (Brinton, 2008) (Fig. 1). Intact mitochondrial function is essential for cell energy homeostasis and survival and mitochondrial failure has been implicated in the etiology of several neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease and Huntington's disease, among others (Simpkins et al., 2005, 2008). There is evidence suggesting that mitochondrial function is regulated by estrogens. Estrogen receptor β is localized in mitochondria in a variety of cell types, including neurons (Yang et al., 2004; Simpkins et al., 2008). Thus, the neuroprotective effects of SERMs may depend in part on activation of mitochondrial estrogen receptor β . Although this finding has been controversial (Schwend and Gustafsson, 2006; Yang et al., 2006), there is some evidence suggesting that estrogen receptor β activation in mitochondria may inhibit apoptotic signaling (Hsieh et al., 2006). However, the role of mitochondrial estrogen receptor β in the neuroprotective actions of SERMs remains to be adequately explored.

In addition to possible effects of estrogenic compounds on mitochondria via estrogen receptors, another mechanism for estrogenic modulation of mitochondrial function has been postulated.

It has been proposed that estrogen analogues with phenol groups are able to intercalate into mitochondrial membranes and inhibit lipid peroxidation reactions (Simpkins et al., 2005). This is the basis for a very interesting development: estrogen-like molecules with one or more phenol rings, which share the antioxidant properties of 17 β -estradiol but that do not activate estrogen receptors in the reproductive tract. These are the so-called non-feminizing estrogens, such as 17 α -estradiol and estratriene derivatives, which have potent neuroprotective effects (Dykens et al., 2003; Perez et al., 2005; Simpkins et al., 2004, 2005; Jung et al., 2006; Wang et al., 2006). Interestingly, 17 α -estradiol, has been demonstrated to be present at high levels in the mammalian brain (Toran-Allerand et al., 2005). Levels of 17 α -estradiol do not decline following gonadectomy and adrenalectomy, and all of the known enzymes required for synthesis of this estrogen are present within the brain, suggesting that this enantiomer is produced in brain tissue.

Role of glial cells in the neuroprotective actions of SERMs

In addition to direct hormone effects on neurons, estradiol, SERMs and non-feminizing estrogens may also exert neuroprotective effects by altering the physiology and morphology of astrocytes (Ciriza et al., 2004). Some neuroprotective SERMs may have cellular specificity and exert estrogenic effects differentially in specific subsets of neurons and glia and endothelial cells (Ciriza et al., 2004), and each of these cell types has been shown to express estrogen receptors. In response to injury, there is a marked increase in expression of the α form of estrogen receptor, and possibly also the β form, in reactive astrocytes (Blurton-Jones and Tuszynski, 2001; Garcia-Ovejero et al., 2002). Together with the injury-induced upregulation of estrogen receptors in neurons (Dubal et al., 1999, 2006) and of the estradiol synthesizing enzyme aromatase in astrocytes (Garcia-Segura 2008), these results suggest that estrogen receptor activation represents an endogenous protective mechanism that may be exploited with exogenous treatments. 17 β -Estradiol and estrogenic compounds may promote neuronal survival inducing astrocytic release of growth factors, such as transforming growth factor β 1 (TGF β 1) or IGF-I (Sortino et al., 2004; Dhandapani et al., 2005; Mendez et al., 2006). In addition, estrogenic compounds may affect brain responses to pathological conditions by regulating reactive gliosis and the expression of molecules in reactive astroglia that are part of the response of astrocytes to injury (Garcia-Ovejero et al., 2005). In addition, 17 β -estradiol in cultured astrocytes reduces activation of NF-kappaB induced by amyloid A beta (1–40) and lipopolysaccharide (Dodel et al., 1999). Since NF-kappaB is a potent immediate-early transcriptional regulator of numerous pro-inflammatory genes, the hormonal regulation of NF-kappaB in astrocytes may play a crucial role in the neuroprotective effects of estrogenic compounds.

Other brain cells that are highly relevant for the neuroprotective and anti-inflammatory effects of estrogenic compounds are microglia (Drew and Chavis, 2000; Lei et al., 2003; Suuronen et al., 2005; Tapia-Gonzalez et al., 2008; Vegeto et al., 2006, 2008). Microglial cells are specialized macrophages of the brain that are activated by neuronal injury and are involved, directly or indirectly, in most neurological disorders. Several estrogenic compounds, including the SERMs tamoxifen and raloxifene, reduce microglia activation and the production of inflammatory mediators by microglia in response to various inflammatory stimuli and in animal models of Alzheimer's disease (Drew and Chavis, 2000; Suuronen et al., 2005; Tapia-Gonzalez et al., 2008; Vegeto et al., 2006, 2008).

Finally, it is important to note that some cells may respond to estradiol and SERMs even in the absence of estrogen receptors, provided that they receive appropriate signals from cells that do express estrogen receptors. The great degree of cell-to-cell communication characteristic of the nervous system supplies the appropriate networks for such signaling: neurons expressing estrogen receptors, for example, intercommunicate extensively with cells devoid of estrogen

receptors as well as with other cells that do express estrogen receptors, such as neurons or glial cells, and these may express estrogen receptor α only, estrogen receptor β only or both estrogen receptors. The final functional outcome of SERMs in neuroprotection and repair will depend on the integration of the intercellular signaling in these neuronal-glial networks (Dhandapani and Brann, 2003; Sortino et al., 2004; Dhandapani et al., 2005; Garcia-Ovejero et al., 2005).

Conclusions

Estrogen receptors are a target for therapeutic approaches to prevent cognition decline with aging or the development of affective and cognitive disorders after menopause. New selective modulators for estrogen receptors, such as arzoxifene, bazedoxifene, lasofoxifene, and ospemifene, among others, are being tested in clinical trials (Shelly et al., 2008). Before the therapeutic use of these drugs as neuroprotectants is considered, it is essential to learn much more about the expression and regulation of estrogen receptors and transcriptional cofactors in the aging brain and also about the impact of aging on the convergence of estrogen receptor signaling with other signaling pathways. Additional screening will be required to adequately determine the neuroprotective potency of available selective steroid receptor modulators and other estrogenic compounds, such as non-feminizing estrogens, that do not activate estrogen receptors. The promising potential of these molecules, and others, for the treatment of different forms of neurodegeneration in experimental models merits a sustained research and development effort.

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Fig. 1.

Estrogenic compounds can bind the intracellular estrogen receptors (ER α and ER β) which are then translocated to the cell nucleus (1). There they recognize specific estrogen response elements (ERE), recruit additional cofactors and modulate gene expression. Alternatively, estrogen receptors (ERs) can interact with other transcription factors (TF), regulating the expression of genes with different response elements (RE). Estrogen receptors can also be phosphorylated by receptor tyrosine kinases (RTK) (2); this phosphorylation affects the receptor activity, which can be activated and translocated to the nucleus even in the absence of ligand. On the other hand, both cytosolic and membrane bound estrogen receptors can transactivate receptor tyrosine kinases or receptor associated kinases, modulating intracellular cascades. Membrane estrogen receptors (mbER) are variants of intracellular receptors, that can be attached to the plasma membrane, where directly interact with signaling molecules (3) like PI3K, activating PI3K and MAPKs pathways, or with other receptors, such as metabotropic glutamate receptors (mGluR1) (4). Estrogens and derivatives can also bind G-protein coupled receptors (GPCR) (5). All these signals through plasma membrane activate intracellular cascades that end in cytosol targets and transcription factors and cofactors that modulate gene expression. Finally, estrogenic compounds can find receptors in specific organelles, such as mitochondria (6) or in very specialized cellular structures, such as synapses, or can buffer free radicals due to their anti-oxidant properties (7).