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# Estrogen receptor agonists for attenuation of neuroinflammation and neurodegeneration

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## Abstract

Recent results from laboratory investigations and clinical trials indicate important roles for estrogen receptor (ER) agonists in protecting the central nervous system (CNS) from noxious consequences of neuroinflammation and neurodegeneration. Neurodegenerative processes in several CNS disorders including spinal cord injury (SCI), multiple sclerosis (MS), Parkinson's disease (PD), and Alzheimer's disease (AD) are associated with activation of microglia and astrocytes, which drive the resident neuroinflammatory response. During neurodegenerative processes, activated microglia and astrocytes cause deleterious effects on surrounding neurons. The inhibitory activity of ER agonists on microglia activation might be a beneficial therapeutic option for delaying the onset or progression of neurodegenerative injuries and diseases. Recent studies suggest that ER agonists can provide neuroprotection by modulation of cell survival mechanisms, synaptic reorganization, regenerative responses to axonal injury, and neurogenesis process. The anti-inflammatory and neuroprotective actions of ER agonists are mediated mainly via two ERs known as ERα and ERβ. Although some studies have suggested that ER agonists may be deleterious to some neuronal populations, the potential clinical benefits of ER agonists for augmenting cognitive function may triumph over the associated side effects. Also, understanding the modulatory activities of ER agonists on inflammatory pathways will possibly lead to the development of selective anti-inflammatory molecules with neuroprotective roles in different CNS disorders such as SCI, MS, PD, and AD in humans. Future studies should be concentrated on



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finding the most plausible molecular pathways for enhancing protective functions of ER agonists in treating neuroinflammatory and neurodegenerative injuries and diseases in the CNS.

**Keywords**

estrogen receptor agonists; inflammation; neurodisorders; neuroprotection

## 1. Introduction

Estrogens are involved in the development and maintenance of normal reproductive functions. They also play very important roles in the immune system as well as in the central nervous system (CNS) in human body (Warner and Gustafsson, 2014). Especially, 17β-estradiol (E2) is the most potent estrogen produced in the human body. Estrone and estriol, the other two active metabolites of E2, are found to be less potent than E2 on estrogen receptors (ERs). Recent studies indicated the organ specific roles of these two estrogen metabolites (Watson et al., 2008).

Elwood Jensen and co-workers first discovered the estrogen binding protein known as ERα (Jensen et al., 1962). The first ERα knockout mouse was created in 1993 (Lubahn et al., 1993) but the knockout mouse showed normal functions of life. Following characterization of ERβ, researchers speculated that ERβ would imitate the action of ERα and support the survival of the ERα knockout mouse. Then, ERβ and double ERαβ knockout mice were created to solve the question (Krege et al., 1998). All single and double knockout studies involving ERα and ERβ showed the drastic impairment of reproductive function without much alteration in normal functions life (Couse et al., 1999). Recently, ER agonists have clearly been shown to possess neuroprotective effects in spinal cord injury (SCI) in rats (Sribnick et al., 2009a). Reduced levels of estrogen are associated with the development of neurodegenerative disorders such as Alzheimer's disease (AD) (Launer et al., 1999; Zandi et al., 2002) and Parkinson's disease (PD) (Currie et al., 2004; Ragonese et al., 2004). Recent clinical trials in post-menopausal women demonstrated deleterious effects of estrogen-based hormone therapy (Lai et al., 2013). So, development of synthetic estrogenic molecules that selectively mimic estrogen can greatly improve the outcomes in the hormone-based therapy (McDonnell et al., 2000). Most synthetic estrogens have been evaluated for their binding affinities to the ERα or ERβ and their ability to regulate ER-dependent transcription in reporter systems (Sun et al., 1999) but their neuroprotective potentials remain to be fully elucidated.

The innate immune responses are regulated by the complex signaling pathways between the immune system and the CNS in the brain (Rivest 2009). Microglia are involved in activation of astrocytes and migration of peripheral immune cells (Voskuhl et al., 2009; Sofroniew and Vinters, 2010) to respond to infection or injury in the brain. Estrogens and ER agonists could modulate the activation of many different cell types of the immune system (Straub, 2007) and the CNS (Spencer et al., 2008; Dumitriu et al., 2010). Recent investigation suggests that estrogens can suppress the activation of microglia and recruit the blood-derived monocytes in rat brain after intracerebroventricular injection of bacterial lipopolysaccharide (LPS) (Vegeto et al., 2003). This investigation also showed an increase

in expression of C3 receptor and matrix metalloproteinase-9 (MMP-9) following LPS exposure (Vegeto et al., 2003). Estrogens can also inhibit expression of pro-inflammatory cytokines such as IL-1β and TNF-α in primary astrocytes following LPS exposure (Lewis et al., 2008). These studies suggest that depending on the signaling mechanisms, estrogens can play dual roles for attenuation of neuroinflammation and neurodegeneration by inhibiting activation of microglia and astrocytes (Fig. 1).

The effects of estrogen and ER agonists are mainly mediated by two genetically distinct receptors, ERα and ERβ, of the nuclear receptor superfamily (Gronemeyer et al., 2004). ERα and ERβ regulate gene expression upon binding to estrogen-responsive elements in target gene promoters, by interfering with other transcription factors, or by modulating a variety of signaling pathways (Schultz et al., 2005). Estrogen and ER agonists are capable of altering the transcription of a large number of genes (Madak-Erdogan et al., 2013) that are known to participate in neuroinflammatory responses in astroglia (Barreto et al., 2009), interneurons (Kritzer 2002), and microglia in frontal cortex (Sierra et al., 2008). Still the involvement of estrogen and ER agonists in regulation of many neuroinflammatory genes in the cerebral cortex remain to be evaluated.

## 2. Estrogen receptors (ERs) and their subtypes

Estrogen and ER agonists modulate cell signaling pathways mainly through binding to ERα and ERβ, which belong to the nuclear receptor family of transcription factors. It is well established that ERα and ERβ harbor evolutionarily preserved and functionally dissimilar domains as well as high degree of specific sequence homology. The DNA-binding domain at the center is the most preserved part, which participates in binding to specific DNA sequence in the promoter region of the target gene. The C-terminal part is used for ligand-binding. The N-terminal part appears to be variable in length as well as in sequence. Otherwise, ERα and ERβ have substantial sequence homology and comparable affinities for binding to estrogen and ER agonists. Both ERα and ERβ are capable of binding to the same DNA sequence in the promoter of the target gene.

The binding of ER agonists to the ERs triggers estrogen signaling pathways in the target cells. ER agonists can also activate different signaling pathways such as PI3K/Akt and MAPK/ERK to provide neuroprotection (Bourque et al., 2012). Upon activation, ERs act as transcription factors and modulate the expression of many estrogen responsive target genes and this process depends on the presence of other signaling molecules in the cells (Nilsson et al., 2001; Katzenellenbogen and Katzenellenbogen, 2002).

The ERα and ERβ genes are located on different chromosomes and code for 66 and 59 kDa proteins, respectively (Enmark et al., 1997). Mutiple splice variants of both ERα and ERβ have been characterized. Different ERs and other receptor isoforms contribute to the complexity of estrogen signaling. Although various splice variants of ERs have been discovered, their biological functions are not yet clearly determined. A recent investigation indicates that determination of functions of different ERα splice variants and their specificity in the cells may be helpful in understanding the estrogen-based therapy in CNS diseases (Ishunina et al., 2013). Majority of ERα variants have variation in 5′-untranslated

region (UTR) but their coding sequence is same. Although some alternative ERβ isoforms are produced in different cells and tissues at different stages (Saji et al., 2002), only the ERβ isoform with 530 amino acids is recognized as the wild-type ERβ in humans (Leygue et al., 1998). Recent investigations indicate that different ERβ isoforms can differently modulate estrogen signaling for regulation of expression of the target gene (Leung et al., 2006; Ramsey et al., 2004). The existence of some common isoforms and species-specific isoforms of ERβ has been reported (Lewandowski et al., 2002). Interactions of different isoforms of ERβ and ERα have not yet been investigated in details. The human ERβ2 isoform is not capable of binding to ligand and does not possess transcriptional ability. It is possible that abolition of transcriptional activity occurs due to dimerization of ERβ2 with ERα (Ogawa et al., 1998).

Unlike other nuclear receptors such as the retinoic acid receptor (RAR) and thyroid hormone receptor (TR), ER ligand cavity can vary in size for estrogen and ER agonists (Brzozowski et al., 1997). Thus, many compounds with diverse molecular structures can bind to ERs. Not only synthetic compounds but also environmental pollutants such as polynuclear aromatic hydrocarbons, phthalate esters, xenohormones, and many pesticides have high affinity for binding to ERs (Bolger et al., 1998). Phytoestrogens, which are estrogen-like compounds derived from plants, have estrogenic properties when used in humans and ranch animals (Oostenbrink et al., 2000). Some of the phytoestrogens can modulate the activities of endocrine signaling pathways and thus they are described as the endocrine disruptors. Exposure to endocrine disruptors may be related to induction of breast cancer and impairment of reproductive function (Witorsch, 2002a). In contrast, many other studies suggest that dietary phytoestrogens in soy and grain products can reduce the risk of some hormone-associated cancers (Witorsch, 2002b). Genistein, which is an abundant phytoestrogen in soy, has much higher selectivity for ERβ than for ERα and can inhibit cancer growth (Barkhem et al., 1998). Based on various exciting results from recent investigations, it appears that genistein is on its way to be an important replacement for estrogen in the treatment of cancer, cardiovascular incidences, diabetes, inflammatory diseases, and metabolic diseases (Heldring et al., 2007; Rimbach et al., 2008; Węgrzyn et al., 2010). These studies suggest that careful use of ER agonists including phytoestrogens can engage specific ERs for providing therapeutic benefits in a number of challenging diseases in humans.

## 3. Potential therapeutic effects of ER agonists in CNS disorders

Many recent investigations indicated that ER agonists play crucial roles in enhancing memory and cognition and ameliorating neuroinflammation and neurodegenerative diseases. But the beneficial role of ER agonists in acute injury has only recently been a focus of intense investigation. Previous acute injury experiments were performed using males to determine the initiation, progression, and pathophysiological mechanisms with the assumption that results obtained from these studies using males might be applicable to females as well. But recent results suggest that both sex and ER agonists are equally important in producing specific outcomes from the treatment of neurodisorders. Various investigations further showed that females are less affected due to acute insults such as brain ischemia (Green and Simpkins, 2000; Hurn and Macrae, 2000), traumatic CNS injury (Roof

and Hall, 2000), hypoxia (Saiyed and Riker, 1993), and toxicity induced by a drug (Cadet et al., 1994). Some of the recent advances in molecular mechanisms of estrogen and ER agonists mediated attenuation of neuroinflammation and neurodegeneration are being described below.

### 3.1. Traumatic brain injury

Traumatic brain injury (TBI), which is an injury in the brain, causes serious disability and even death. Various studies clearly show that significant gender differences in the occurrence and pathophysiology of TBI do exist. Males have been reported to encounter TBI more frequently than females due to sporting disasters, motor vehicle accidents, combat operations, and street violences. Similarly, occurrence of cerebrovascular stroke (CS) is more frequent in males than the pre-menopausal females (Barrett-Connor and Bush, 1991). The occurrence of CS in older post-menopausal females is almost same when compared with the age-matched males (Wolf, 1990). Following ischemia, hypoxia, or TBI, young female rodents could survive longer than their male counterparts, as shown by number of studies (Zhang et al., 1998; Carswell et al., 1999; Hall et al., 1998). Administrations of ER agonists can provide neuroprotection against different type of neuronal injury in vitro and in vivo and the treatments reduce the extent of injury and, in some cases, decrease mortality and behavioral deficiency (Shao et al., 2012; Schreihofer and Ma, 2013). Various investigators have examined many ER agonists with different doses. ER agonists have been administered at physiological and pharmacological levels at different time points before or after TBI. Results indicated that lower physiological concentrations of ER agonists should be administered before the injury to exert protective actions, while pharmacological doses of ER agonists may be protective even when administered at 3 h following induction of injury (Yang et al., 2000). Although ER agonists provide neuroprotection against neural injury, the precise molecular signaling pathways by which they achieve neuroprotection still remain mostly unclear. Studies in numerous cell culture models have indicated inhibition of the neuronal death after treatment with the ER agonists following toxic insults. Similarly, many animal model studies demonstrated that different doses of ER agonists could produce different outcomes in toxic insults such as oxidative stress, glucose deprivation, hypoxia, and physical injury (Wise et al., 2001). More investigations in animal models will be needed to establish the optimum doses of ER agonists in the treatment of TBI and other injuries in the brain.

### 3.2. Spinal cord injury

Spinal cord injury (SCI) is a highly complex CNS injury that can be associated with different levels of contusion, axonal damage, oxygen depletion, hemorrhage, and pathophysiological mechanisms. Primary injury to the spinal cord causes the immediate insults to the neurons, axons, glial cells, and blood vessels at the site of injury (Ray et al., 2003; Samantaray et al., 2010; Ray et al., 2011). Secondary injury involves devastating pathophysiological mechanisms including increase in reactive oxygen species (ROS), reperfusion, glutamate concentration, and mitochondrial damage (Carlson et al., 1998; Mills et al., 2000). Mitochondrial damage in SCI alters $Na^+/K^+$-ATPase activity, increases intracellular $Ca^{2+}$ level, and activates glutamate receptors (Agrawal et al., 2000; Li et al., 2000; Wingrave et al., 2004). Increase in intracellular free $Ca^{2+}$ level following SCI leads to

activation of the $Ca^{2+}$-activated protease calpain and phospholipases (Dhillon et al., 1999; Ray et al., 2003). Upon activation, calpain can degrade a number of cytoskeletal proteins such as neurofilament proteins, α-spectrin, and myelin basic protein (Ray et al., 2003). A sustained activation of calpain can cleave calpastatin, which is an endogenous calpain inhibitor, resulting in an uncontrolled calpain mediated proteolysis in tissue (Pang et al., 2003). Altogether these effects cause biochemical and metabolic changes in the spinal cord leading to neural cell death and progressive tissue damage (Sribnick et al., 2009a). Both primary and secondary injury mechanisms of SCI can result in significant neurological deficits, permanent paralysis, or even death of the SCI victim.

Recent studies suggest that estrogen and ER agonists can protect neurons and inhibit axonal degeneration during early phase (48 h) following SCI in rats (Sribnick et al., 2005; Sribnick et al., 2009a). Similar outcomes have been observed in ischemia and TBI (Dubal et al., 2001; Jover et al., 2002). Experimental TBI in animal models indicate that TBI females recover better than TBI males after treatment with ER agonists (Bayir et al., 2004). A number of cell culture studies established the impressive neuroprotective potential of ER agonists in glial cells as well as in neurons following exposure to oxygen free radicals or glutamate toxicity (Sribnick et al., 2004; Das et al., 2005; Sribnick et al., 2009b). Other studies also confirm that ER agonists can be used as potent anti-oxidant (Moosmann and Behl, 1999) and anti-inflammatory agents (Dimayuga et al., 2005) to provide functional neuroprotection. We recently reported that miR-7-1 potentiated ER agonists for functional neuroprotection in VSC4.1 motoneurons (Chakrabarti et al., 2014). Indeed, the multi-action characteristics of ER agonists make them very attractive therapeutic agents for treatment of SCI.

### 3.3. Cerebral ischemia

Cerebral ischemia or stroke is the sudden loss of CNS function due to inhibition in the blood supply to the brain. Low physiological levels of estrogen can dramatically reduce overall infarct size in the middle cerebral artery with permanent occlusion (Dubal et al., 1998), indicating the therapeutic potentials of estrogen and ER agonists in cerebral ischemia. The risk of stroke treatment outcomes clearly depend on the gender of the stroke victims (Hurn and Macrae, 2000; McCullough et al., 2001). Young women with normal endogenous levels of estrogen have significantly less risk and severity of stroke than age-matched men. Both the vasoprotective and neuroprotective roles of estrogen have been documented in experimental cerebral ischemia (McCullough et al., 2001). It is interesting to note that ER agonists through activation of ERα and ERβ can exert their vasodilatory and neuroprotective effects in systemic circulation (Luksha et al., 2009). Recently, it has been reported that another G protein-coupled ER, called GPR30, is involved in acute vasodilatory effect of ER agonists in arteries and veins in humans (Haas et al., 2007; Murata et al., 2013). Another recent study suggests that GPR30 agonists have the potential to reduce neuronal injury following global cerebral ischemia (Kosaka et al., 2012). Hyper-activation of N-methyl-d-aspartate receptors (NMDARs) has been observed in different neurodegenerative conditions (Vizi et al., 2013). NMDARs consist of three different subtypes: NR1, NR2, and NR3. The NR2B subunit is observed in the extra-synaptic sites and it plays a significant role in glutamate-mediated neuronal cytotoxicity in both cell culture and animal models (Liu and

Zhao, 2013). Neuroprotective potential of estrogen has been reported to be partially mediated by GPR30 and the subsequent down regulation of NR2B-containing NMDARs (Liu et al., 2012). But, the details about GPR30 mediated vasoactive effects in cerebral microcirculation still remain unclear (Murata et al., 2013). The molecular pathways leading to vessel dysfunction during cerebral ischemia and reperfusion include inhibition of $K^+$ channels (Bari et al., 1996), enhanced oxidative stress (Hossmann et al., 2006), and reduced level of nitric oxide (NO) (Cipolla et al., 2008). Studies suggest that ER agonists are capable of improving microvascular dysfunction by preserving the process of vasodilation (Watanabe et al., 2001) or by reducing oxidative stress (Stirone et al., 2005) in experimental cerebral ischemia.

### 3.4. Multiple sclerosis

Multiple sclerosis (MS) is a heterogeneous neuroinflammatory demyelinating autoimmune disease triggered by T helper 1 (Th1) and Th17 cells. Current studies also clearly indicate MS as a neurodegenerative disease. Studies performed in many different laboratories have shown that the clinical severity of both active and adoptive experimental autoimmune encephalomyelitis (EAE), which is an animal model of MS, is reduced by treatment with ER agonists in several types of mouse models (Bebo et al., 2001; Ito et al., 2001; Liu et al., 2002; Liu et al., 2003; Subramanian et al., 2003). Estriol can effectively reduce the severity of the EAE in animals when administered after disease onset (Kim et al., 1999). Estriol has been shown to inhibit a number of inflammatory cytokines such as IFN-γ, TNF-α, IL-2, and IL-6 in the 6 to 8 weeks old C57BL/6 mice (Palaszynski et al., 2004). The immunomodulatory effects of ER agonists influence T cell differentiation and effector functions including the expansion of the $CD4^+CD25^+$ T regulatory (Treg) cells in EAE animals (Polanczyk et al., 2004). Estrogen and ER agonists can also modulate the functions of many different organ systems including the immune system. ER agonists have also been shown to induce apoptosis in T cells through activation of Fas-Fas ligand pathway, thereby causing immunosuppression (Do et al., 2002; Singh et al., 2012). Estrogen can influence development of $CD4^+$ T cell subpopulations and function through regulation of cytokine profiles (Pernis et al., 2007). It also regulates the expression of adhesion and accessory molecules on endothelial cells and alters leukocyte migration. Low doses of estrogen have been shown to enhance antigen-specific Th1 and Th17 cell responses as well as several other IFN-γ-producing cells via differential activation of MAPK, NF-κB, and AP-1 signaling pathways (Kassi and Moutsatsou, 2010). It is believed that ERα, but not ERβ, is necessary for the enhanced estrogen-driven Th1/Th17 cell responsiveness (Fig. 1). Estrogen may also influence $CD8^+$ T cells and multiple signaling cascades through cytosolic $Ca^{2+}$ influx. Although estrogen has multiple roles in inflammatory diseases, other ER agonists also exert their anti-inflammatory and neuroprotective roles to prevent inflammation and autoimmunity in the CNS. Antigen presenting cells (APCs) such as dendritic cells (DCs) and macrophages may play important roles in connecting the innate immune system with the adaptive immune system. A recent study indicated that endogenous estrogen level can modulate the number of APCs (Nalbandian and Kovats, 2005). ER agonists can regulate activities of T cells through direct involvement of APC functions. Studies have shown that splenic DCs isolated from estrogen-treated animals produce lower levels of TNF-α, IFN-γ, and IL-12 upon LPS exposure, while macrophages produce decreased levels of TNF-α

(Flohé et al., 2008). One of the major roles for ERα signaling in T lymphocytes is the induction of anti-inflammatory effects of estrogen and protection against CNS inflammation. Because estrogen treatment provides protective effects in EAE animals, efficacy of estrogen and ER agonists are currently being evaluated in clinical trials for treatment of MS patients.

### 3.5. Parkinson's disease

Parkinson's disease (PD) is a debilitating movement disorder that is mainly characterized by the irreversible and selective degeneration of the dopaminergic neurons in the substantia nigra pars compacta (Hornykiewicz, 1989). There is no effective treatment for PD although L-dopa is an impressive choice in the treatment of some PD patients. All other current medications for PD are symptomatic treatments that hardly prevent the progression of PD. An important observation is highly notable that ER agonists modulate the dopaminergic neurotransmission and may be used to alleviate major symptoms of PD (Session et al., 1994; Giladi et al., 1995). Another study reported that estrogen therapy could lower the severity of initial phase of PD at least prior to administration of L-dopa in PD women (Saunders-Pullman et al., 1999), indicating that estrogen and ER agonists could be useful therapy in PD patients. Inhibition of neuroinflammatory signaling molecules and blockage of neurodegenerative pathways by estrogen and ER agonists may be promising therapeutic approach against PD.

So far, several clinical trials have been reported showing no significant effect (Strijks et al., 1999) or a moderate anti-parkinsonian effect (Blanchet et al., 1999) of estrogen therapy in PD. Hence, the exact role of estrogen on the survival of dopaminergic neurons in humans still remains a mystery. However, some PD animal model studies with newer selective ER modulators (SERMs) like raloxifene supported both pro-dopaminergic and anti-dopaminergic activities of ER agonists in parkinsonism. Many recent reports indicate that incidence of PD is higher in men than in women (Marder et al., 1996; Bower et al., 1999; Baldereschi et al., 2000; Bower et al., 2000), while another study shows existence of no such sex difference in occurrence of PD (de Rijk et al., 1995). Obviously, more studies are needed to resolve this controversy. It should be noted that during progression of PD, men manifest more parkinsonian motor features or dyskinesia than women do (Lyons et al., 1998). Treatment with ER agonists can inhibit development of dementia (Marder et al., 1996), indicating efficacy of ER agonists in brain disorder. While no proven mechanism yet exists for neuroprotective action of estrogen, it is highly plausible that estrogen may reduce oxidative stress and inhibit mitochondrial dysfunction so as to prevent progression of pathophysiology in PD (Numakawa et al., 2011). Estrogen can prevent degeneration of dopaminergic neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrapyridine (MPTP)-induced PD animal brain (Numakawa et al., 2011). While the mechanism responsible for degeneration of dopaminergic neurons in MPTP animal model of PD is unclear, oxidative stress and neuroinflammation are thought to play key roles in ultimate demise of the nigrostriatal dopaminergic neurons. Calpain is a proteolytic enzyme that is activated in response to increases in intracellular free $Ca^{2+}$ and oxidatative stress, both of which are presumed to be present at high levels in dying dopaminergic neurons in MPTP animal model of PD. In fact, recent results indicate a significant role of calpain mediated proteolysis in degeneration and loss of dopaminergic neurons in an animal model of PD (Crocker et al., 2003). It will be

interesting to examine whether ER agonists can provide neuroprotective functions through regulation of expression of the $Ca^{2+}$-binding protein and calpain so as to prevent loss of dopaminergic neurons in the animal model of PD.

### 3.6. Alzheimer's disease

Alzheimer's disease (AD) is characterized by deficiencies in memory and cognition due to degeneneration of mostly hippocampal neurons in the old people. It is the most common cause of dementia, which impairs daily life and activities due to abnormal brain functioning and behavioral difficulties in the AD patients. Currently available symtomatic treatments do not prevent pathogenesis in AD patients. So, innovative and novel therapeutic agents are urgently needed for proper treatment and inhibition of pathogenic mechanisms in AD patients. The neuroprotective actions of ER agonists in AD are supposed to be regulated by activation of ERs in different neurons in different areas of the brain. Both ERα and ERβ subtypes are widely distributed in the hippocampus, frontal cortex, and amygdala regions (Shughrue et al., 1997; Shughrue and Merchenthaler, 2000; Hart et al., 2001). A very recent study identified alteration in normal distribution of ERs in hippocampal neurons in AD (Liu et al., 2008). A shift of ERα localization from the nucleus to the cytoplasm has been shown to inhibit the development of AD pathology in transgenic mice (Jorm et al., 1987) as well as in humans (Henderson et al., 1994). Folstein test scores in women with terminal stage AD showed an increase in ERα level in the frontal cortex (Kawas et al., 1997). Also, allele differences in ERα appear to correlate well with a high-risk for development of AD in women who are already suffering from Down's syndrome (Schupf et al., 2008). When compared with the same age control groups, immunoreactivity of ERβ was found to be increased in the hippocampal cells in AD (Savaskan et al., 2001). Upregulation of ERs in hippocampus of AD patients should provide an advantage to the therapeutic approach using ER agonists. Collectively, recent investigations suggest that the levels of expression of the ERα and ERβ can play important roles for ER agonists for inhibition of neuroinflammation and achieving neuroprotective functions in the AD brain. Several interesting studies have already described these phenomena in details (Lee et al., 2014).

## 4. Mechanisms of action of ER agonists for neuroprotection

As mentioned previously, both ERα and ERβ are involved in estrogen mediated neuroprotection. Selective expression of ERα could restore protective action of estrogen against amyloid-β (Aβ) peptide in HT22 cell line, suggesting a prominent role for ERα in estrogen mediated neuroprotection (Kim et al., 2001). The selective ERα agonist (propylpyrazole triol, PPT) and ERβ agonist (diarylpropionitrile; DPN) are supposed to show similar neuroprotective actions in culture studies. But a previous report showed higher neuroprotective potential of the ERα agonist PPT than the ERβ agonist DPN (Behl et al., 1995). In contrast, another study with primary neuron culture showed comparable levels of neuroprotection by estrogen and selective ER agonists against Aβ peptide mediated neurodegeneration, indicating the contribution of both ERα and ERβ in neuroprotection (Corder et al., 2004). Some other investigations showed that both PPT and DPN can provide neuroprotection against glutamate toxicity by increasing the expression of the anti-apoptotic Bcl-2 protein and also modulating the stress kinase signaling pathways (Zhao et al., 2007;

Zhao and Brinton, 2007). These results suggest that DPN has a higher $Ca^{2+}$ dependency for its activity than other ER agonists (Zhao and Brinton, 2007). Altogether, recent reports strongly imply that both ERα and ERβ are involved in achieving significant neuroprotection by the ER agonists against different neurodisorders through activation of various cell survival signaling pathways.

## 5. Benefits and limitations of selective ER modulators (SERMs)

The mode of action of ER agonists in different neurodisorders depends mostly on the presence of ERs. Therapeutic strategy with SERMs can be another promising option for the treatment of neurodegenerative disorders. Some synthetic and natural SERMs like tamoxifen, raloxifene, or bazedoxifene (Mickley and Dluzen 2004; Zhao et al., 2005; Kokiko et al., 2006; Zhao et al., 2006) and genistein (Azcoitia et al., 2006) are neuroprotective (Table I). New neuroprotective SERMs (Neuro-SERMs) may be developed to avoid feminizing effects and specifically target the nervous system to promote cognitive function and to reduce the risk of neurodegenerative diseases (Brinton., 2004, Zhao et al., 2005).

Most of the investigations have so far been focused on tamoxifen and raloxifene for developing effective SERMs against neurodegenerative diseases (Table I). Further studies are needed in animal models with new SERMs like lasofoxifene, bazedoxifene, arzoxifene, and ospemifene to identify an effective agent against neurodegenerative diseases. Bazedoxifene can provide neuroprotection against kainic acid toxicity in rat hippocampal neurons (Kulkarni et al., 2013). Also, combination therapy with ospemifene and bazedoxifene can inhibit inflammatory response in astrocytes (Cerciat et al., 2010). Further studies are needed to uncover the neuroprotective efficacy of SERMs (Azcoitia et al., 2006; Schreihofer and Redmond, 2009).

Clinical application of SERMs as neuroprotective agents will require better permeability of the drug molecules so as to cross the blood-brain-barrier in the CNS. Many investigators are actively working to overcome the current limitations of SERMs to increase their clinical applicability. SERMs with higher affinity to the ERs are also under intense investigation to identify an effective neuroprotective agent (Brinton, 2004; Zhao et al., 2005). One such SERM is 7α-[(4R,8R)-4,8,12-trimethyltridecyl]estra-1,3,5-trien-3,17β-diol that contains the combined structures of vitamin E and estrogen. This molecule has been neuroprotective in rat primary hippocampal neurons and it is capable of binding to both ERα and ERβ (Zhao et al., 2007). Non feminizing analogs of estrogen are other interesting molecules, which are also under intense investigation (Petrone et al., 2014). Other molecules such as ent-17-desoxyestradiol, 17α estrogen, ent-estrogen, and 2-adamantylestrone also show neuroprotective effects in animals with neurodegenerative conditions (Jung et al., 2006; Wang et al., 2006).

Although recent investigations have identified several important molecular targets of ER agonists and SERMs in the CNS in humans, their precise molecular mechanisms of action remain mostly unknown. It has been suggested that ER agonists modulate different signaling pathways involing MAPK, PI3K/Akt, CREB, and NF-κB. In general, ER agonists and

SERMs can exert their cell specific neuroprotective efficacy by modulating neuronal death, remyelination, and inhibiting chronic pro-inflammatory responses.

## 6. Conclusion and future direction

Estrogen and ER agonists work mainly via ERα and ERβ for mediation of their antiinflammatory and neuroprotective effects in many CNS injuries and diseases. Currently, cell culture and animal model studies suggest that ER agonists hold great promise for amelioration of the devastating consequences of several neurodisorders in humans. In addition to ER agonists, vigorous research is focused on SERMs for identification of the most appropriate therapeutic agents for treatment CNS injuries and diseases in humans in the future. Further studies are needed to establish the exact molecular mechanisms of ER agonists and SERMs for inhibition of neuroinflammation and neurodegeneration in diverse neurodisoders in the human brain and spinal cord.

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## Highlights

- Estrogen receptor (ER) agonists play crucial roles in the immune system and the CNS
- Cell signaling pathways are modulated by ER agonists via binding to ERα and ERβ
- ER agonists can promote transcription of a large number of neuroprotective genes
- Neuroinflammation and neurodegeneration in the CNS are prevented by ER agonists
- ER agonists play significant roles in enhancing memory and cognition

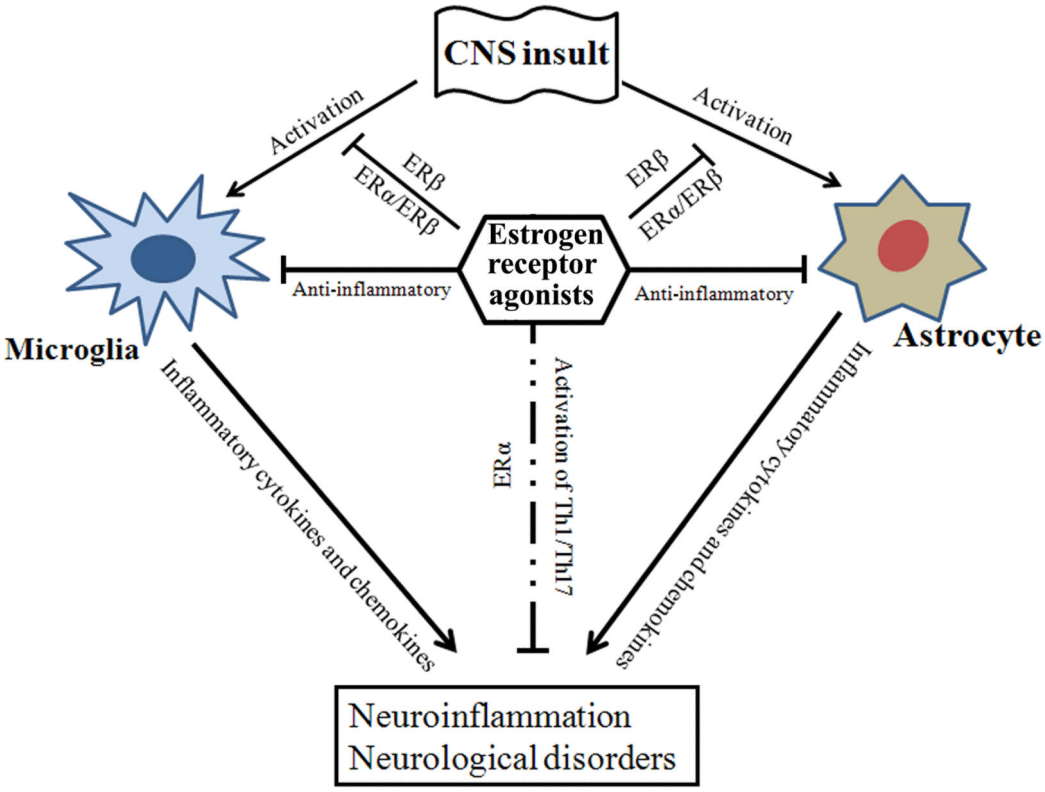


**Fig. 1.**

A schematic representation of anti-inflammatory roles of estrogen and ER agonists in neurodisorders. Insults to the CNS lead to overactivation of microglia and astrocytes. Activated microglia and astrocytes can release pro-inflammatory cytokines and chemokines to induce neuroinflammation to promote pathogenesis in different neurodisorders. Treatment with ER agonists can be useful to inhibit the activation of microglia and astrocytes after the CNS insults. Estrogen driven Th1/Th17 cell response is thought to be carried out via involvement of ERα.

## Table 1
### Estrogen and SERM derivatives examined for potential neuroprotective functions

| Estrogen and SERM derivatives | Estrogen or SERM | Functions | References |
|---|---|---|---|
| Estrogen derivatives | 17β-Estradiol | Antioxidant, neuroprotective | Chakrabarti et al., 2014; Mosquera et al., 2014 |
| | 17α-Estradiol | Inhibits GABA receptor-induced cell loss | McClean and Nuñez, 2008; Rakkestad et al., 2014 |
| | Estriol | Reduces the disease symptoms in multiple sclerosis (MS) | Sicotte et al., 2002; Ziehn et al., 2012 |
| | Equilin | Used in hormone replacement therapy | Sawicki et al., 1999; Okamoto et al., 2010 |
| Triphenylethylene derivatives | Tamoxifen | Neuroprotection to Aβ-induced toxicity | O'Neill et al. 2004; Herrera et al., 2011 |
| | 4-Hydroxy tamoxifen | Neuroprotection to Aβ-induced toxicity | O'Neill et al., 2004; Arevalo et al., 2011 |
| | Droloxifene | Inhibits estrogen mediated neuroprotection | Christian, 2001; Zhao et al., 2005 |
| | Ospemifene | Induces production and release of pro-inflammatory molecules by glial cells | Cerciat et al., 2010; Arevalo et al., 2011 |
| Phytoestrogens | Coumestrol | Protects hippocampal neurons in cerebral ischemia | Castro et al., 2012; Castro et al., 2014 |
| | Daidzein | Decreases cell death and improves synaptic function in oxygen–glucose deprivation (OGD) | Schreihofer and Redmond, 2009; Hurtado et al., 2012 |
| | Equol | Vasorelaxant, anti-oxidant, and neuroprotective in transient focal cerebral ischemia | Jackman et al., 2007; Ma et al., 2010. |
| | Formononetin | Protects neurons from NMDA-induced excitotoxic injury and neurodegenerative disorders in central nervous system | Occhiuto et al., 2008; Occhiuto et al., 2009; Tian et al., 2013 |
| | Genistein | Reduces oxidative stress, hippocampal neuron death, and cognitive defects in neurodegenerative disorders | Azcoitia et al., 2006; Malinowska et al., 2010; Wang et al., 2013 |
| Benzothiophene derivatives | Arzoxifene | GPR30-dependent and ER-independent neuroprotection | Littleton-Kearney et al., 2002; Abdelhamid et al., 2011 |
| | Bazedoxifene | Anti-inflammatory effects in astrocytes, inhibition of IL-6, IFN-ɣ, and NF-κB p65 transactivation | Cerciat et al., 2010; Arevalo et al., 2011 |
| | Raloxifene | Poor bioavailability, ERα dependent but ERβ and GPR30 independent hypoxia induced neuroprotection | Kushwaha et al., 2013; Rzemieniec et al., 2014 |