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Molecular mechanisms involved in the protective actions of Selective Estrogen Receptor Modulators in brain cells

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ABSTRACT

Synthetic selective modulators of the estrogen receptors (SERMs) have shown to protect neurons and glial cells against toxic insults. Among the most relevant beneficial effects attributed to these compounds are the regulation of inflammation, attenuation of astrogliosis and microglial activation, prevention of excitotoxicity and as a consequence the reduction of neuronal cell death. Under pathological conditions, the mechanism of action of the SERMs involves the activation of estrogen receptors (ERs) and G protein-coupled receptor for estrogens (GRP30). These receptors trigger neuroprotective responses such as increasing the expression of antioxidants and the activation of kinase-mediated survival signaling pathways. Despite the advances in the knowledge of the pathways activated by the SERMs, their mechanism of action is still not entirely clear, and there are several controversies. In this review, we focused on the molecular pathways activated by SERMs in brain cells, mainly astrocytes, as a response to treatment with raloxifene and tamoxifen.

1. Introduction

Astrocytes perform essential functions in the brain, such as providing nutrients, recycling neurotransmitters, and maintaining brain homeostasis (Pekny and Pekna, 2014; Sofroniew and Vinters, 2010) and blood-brain barrier (BBB) stability (Chodobski et al., 2011). Besides, astrocytes play a significant function in maintaining physiological brain functions by releasing antioxidant and anti-inflammatory molecules, growth factors, and neurotrophins to the brain milieu (Buffo et al., 2010; Colangelo et al., 2014). Among the more critical functions of astrocytes is the modulation of the immune system, including the regulation of inflammatory proteins expression and formation of glial scars (Sheng et al., 2013) after damage of the central nervous system (CNS) (Dickson, 2012; Nair et al., 2008) (see Figs. 1 and 2).

Despite advances in the study of pathophysiology and testing of many molecules in search of a possible treatment, there are still many diseases such as traumatic brain injury (TBI), spinal cord injury (SCI), Parkinson's disease (PD), and Alzheimer's disease (AD) that do not have a timely and efficient treatment that can halt or reverse the cognitive damage and neuronal dysfunctions. Currently, different compounds have been proposed for the attenuation of reactive gliosis or pathological treatments. Some of these compounds are Selective Estrogen Receptor Modulators (SERMs), Selective tissue estrogenic activity regulators (STEARs), and isoflavones. The SERMs have been reported to exhibit protective effects in the brain (Acaz-Fonseca et al., 2014; O'neill et al., 2004; Rutanen et al., 2003) and are becoming a promising therapeutic alternative because they have shown neuroprotection in several experimental models of injuries and pathologies. Tamoxifen and raloxifene are two SERMS that have been reported to be quite useful in the treatment or protection of the CNS.

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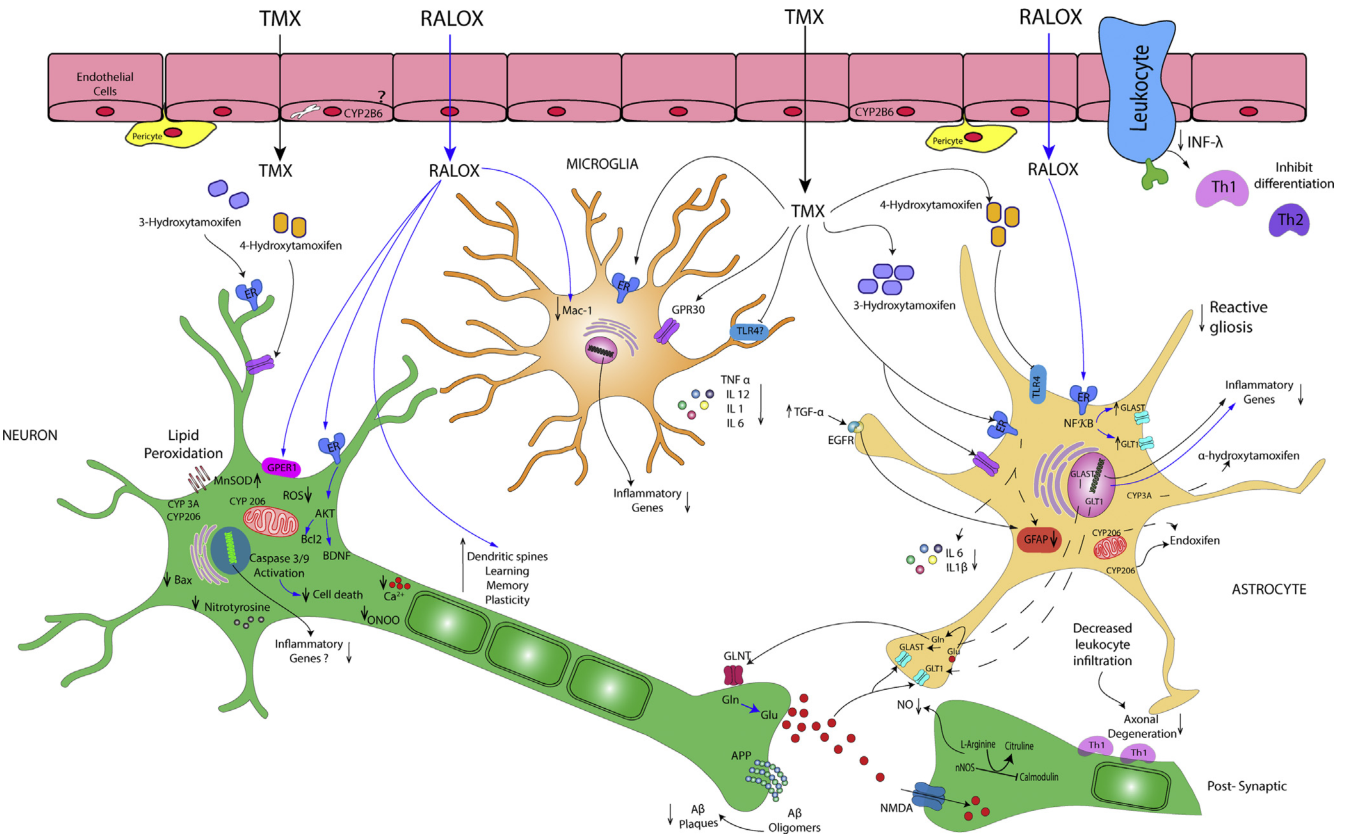

Fig. 1. Neuroprotective actions of tamoxifen and raloxifen under pathological conditions and proposed mechanism of metabolism of tamoxifen in the brain by P450 enzymes. Following brain injury, tamoxifen binds to the classical receptors ERα and ERβ or to membrane receptor such as GPR30. Upon binding, it exerts protective actions by reducing lipid peroxidation, nitrotyrosine levels, ROS formation, Aβ plaques, apoptotic proteins, excitotoxicity and axonal degeneration induced by Th1 and Th2 infiltration. Tamoxifen by acting on ERs decreases microglia activation and reduces TNF, IL1, IL6 and IL12. Tamoxifen also inhibits upregulation of TLR4. In astrocytes, tamoxifen diminishes astrogliosis and GFAP expression by upregulating TGF-α and EGFR expression. Tamoxifen also decreases IL1β, IL6 and inflammatory genes expression. It also induces the expression of glutamate transporters GLUT1 and GLUT2, and anti-apoptotic genes. The neuroprotective actions of tamoxifen might be induced by one of its metabolites as well. Astrocytes and neurons express CYṔs enzymes such as CYP2A6 and CYP3A, whilst endothelial cells do express CYP2B6, in which tamoxifen is metabolized into endoxifen and 4-hydroxytamoxifen. The possible mechanism of action of raloxifene on different brain cells is similar to that reported with tamoxifen. The possible effects of raloxifene are indicated in blue lines in the figure.

It has been shown that tamoxifen, raloxifene, and others SERMs can regulate the morphology and functions of astrocytes, neurons, and microglia by their interaction with estrogen receptors α and β (ERα and ERβ) (Gonzalez et al., 2016; Li et al., 2014). These compounds have also been reported to act via activation the G-protein coupled receptor (GPR30) (Bourque et al., 2014; Gonzalez et al., 2016). The neuroprotective signals stimulate several signaling cascades. For example, tamoxifen acts stimulating several signaling factors including phosphatidylinositide 3-kinases (PIK3)/protein kinase B (Akt), cAMP response element binding protein (CREB)1, cAMP, protein kinase A (PKA) and mitogen-activated protein kinase (MAPK)/estrogen receptors. These factors exert brain protection by reducing (a) the inflammatory responses (Franco Rodriguez et al., 2013), (b) lipid peroxidation and reactive oxygen species (ROS) production (Moreira et al., 2005; Zhang et al., 2007), (c) astrogliosis (Colon et al., 2016), (d) and the infiltration of leukocytes into injury zone (Wei and Ma, 2014). These beneficial effects improve spatial learning and memory (X. Sun et al., 2013), and may promote neuronal survival (Wakade et al., 2008).

Despite the advances in the knowledge of the signaling pathways activated by the SERMs, their effects on different nervous cells and under different pathological conditions are still not entirely clear. In this review, the molecular pathways that occur in different brain cells, mainly astrocytes, are discussed in response to treatment with raloxifene and tamoxifen. In addition, the metabolism and actions of their metabolites on the CNS, as possible therapeutic alternatives, in the context of different brain pathologies are discussed. Also, the use of genetic techniques using DNA recombinase and the tamoxifen-Cre/Lox system have permitted to assess the importance of the use of SERMs in the proliferation and differentiation of brain cells, as well as allowed to advance investigation related to the understanding of the effect of tamoxifen on astrogliogenesis and neurogenesis.

2. Astrocyte, neuron and microglia interactions in neurological pathologies and injuries

The interaction between CNS cells (neurons, astrocytes, and microglia) has an essential role in mediating metabolic processes, supplying nutrients and improving braińs metabolism and function (Allaman et al., 2010). This close relationship induces small variations in the environment and can cause changes in the phenotype of cells, gene expression and intracellular dynamics of Ca^{2+} in the brain (Brawek and Garaschuk, 2017; Farina et al., 2007). These changes trigger a chain of reactions that lead to cellular deterioration and death. For example, microglia under conditions of injury produces and releases several inflammatory and anti-inflammatory mediators, whose effects may result in beneficial or detrimental responses (Carniglia et al., 2013; Szalay et al., 2016). A previous study using microglial ablation in a male mouse model of brain ischemia revealed that inhibition of microglia increased infarct size, and calcium-triggered neuronal loss (Szalay et al., 2016). On the other hand, other study revealed that microglia could also promote synaptogenesis in the hippocampus through the release of interleukin 10 (IL-10), which increased

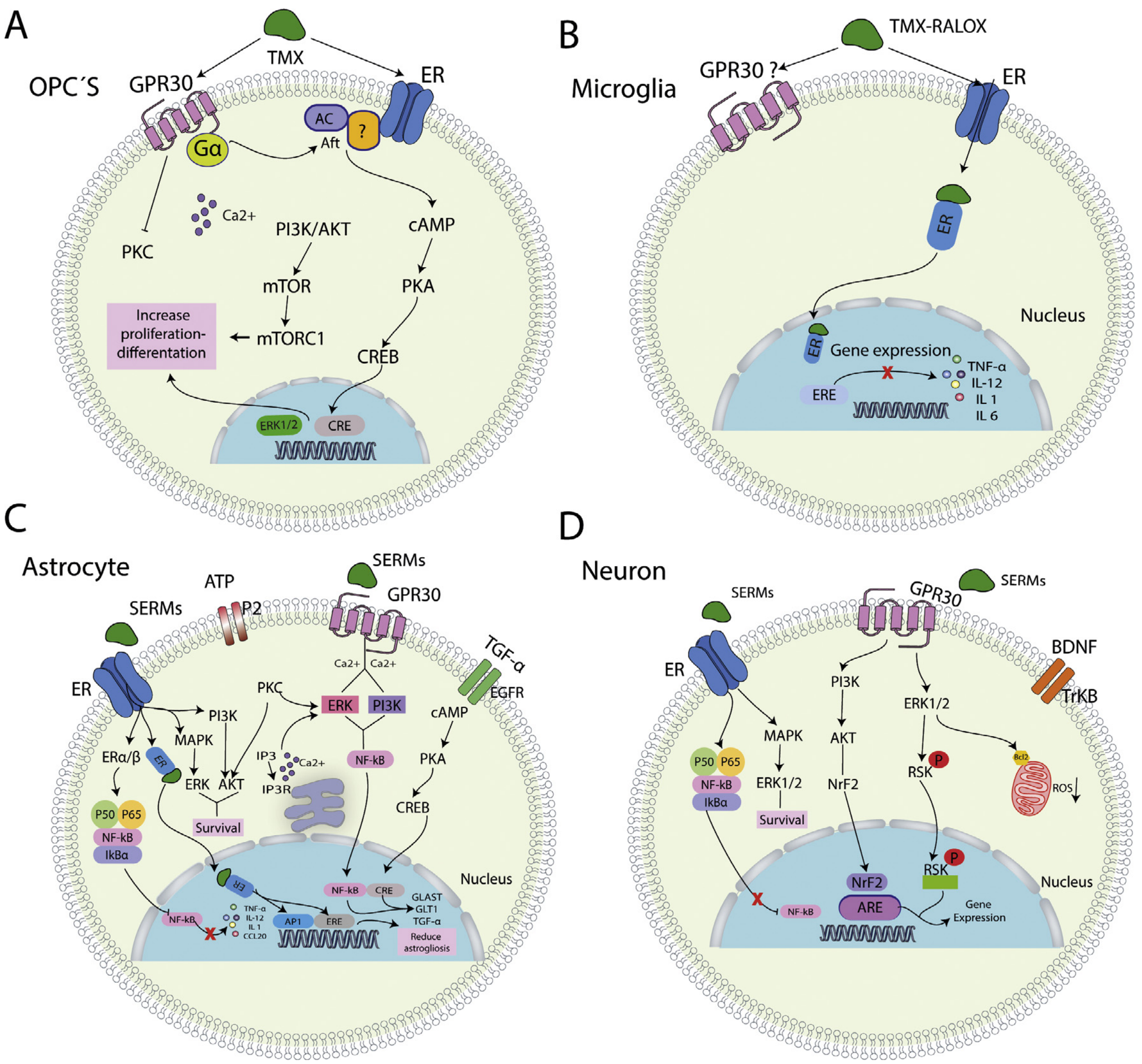

Fig. 2. Molecular actions of tamoxifen in the brain. Tamoxifen binds to ERα, ERβ and GPR30 triggering neuroprotective actions in various cell types promoting survival and differentiation processes. For example, tamoxifen induces differentiation of oligodendrocytes precursors cells (OPĆs) by binding ERs and GPR30 and triggering phosphorylation MAPK/ERK CREB and PI3K/Akt/mTOR signaling pathway (A). In microglia, upon treatment with raloxifene and tamoxifen, the ER dimerizes, enters the nucleus and binds to estrogen response element (ERE) triggering reduction of TNFα, IL1β, IL6 and IL12 (B). In astrocytes, tamoxifen binds to GPR30 and ERs and improves the expression of TGF and GLT1 via CREB, NK-kB and transactivation of epidermal growth factor receptor (EGFR). Tamoxifen also activates ERK 1/2, PI3K, cAMP and PKA pathways. In brain trauma, purinergic receptors (P2) respond to ATP release and activates ERK (C). In neurons, tamoxifen and raloxifene bind to GPR30 triggering a rapid signaling of intracellular Ca^{2+}, activation of PI3K/Akt and Src/ERK/CREB. In addition, both compounds activate Nrf2 and antioxidant response element ARE. Tamoxifen acting on ER inhibits NF-kB p65 nuclear translocation and increases BDNF expression (D).

the number of dendritic spines (Lim et al., 2013).

Current evidence has shown that cooperation between astrocytes and microglia facilitates the disposal of dead cells through phagocytosis that contributes to the reduction of inflammation (Chan et al., 2001). In particular different factors have been identified in microglial cells as the mediators of phagocytosis processes. One of these factors is the MAPK p38 that mediates the migration and accumulation of microglia in the lesion zone, triggering phagocytosis in neuronal cell death induced by the stimulation of the N-methyl-D-aspartate receptor (NMDAR) (Katayama et al., 2012). Likewise, the pro-inflammatory cytokine interferon gamma (IFN-γ) activates different pathways promoting phagocytosis of apoptotic inflammatory cells in the inflamed nervous system (Chan et al., 2001). Though, functional studies have shown that astrocytes have smaller phagocytic capacity than microglia (Magnus et al., 2002). For example, it has been observed male mouse astrocytes engulfing dead cells after TBI, suggesting that it may be a survival mechanism avoiding damage of neurons adjacent to the injured area (Loov et al., 2012). In fact, it has been shown that in amyotrophic lateral sclerosis (ALS), there is an increase in the expression of the receptor transmembrane chemokine CX3C1 receptor 1 (CX3CR1) (D. Sun et al., 2013). These data suggest that, like microglial cells, CX3CL in astrocytes may be mediating phagocytic activity (Cerbai et al., 2012). Another study showed that CX3CL-CX3CR1 signaling inhibited the production of nitric oxide, superoxide (O_2^-), tumor necrosis factor-alpha (TNFα) and pro-inflammatory molecules in astrocyte and microglia in co-culture (Mattison et al., 2013). Interestingly, in another report, the chemokines CX3CL1 and CXCL16 were demonstrated as instrumental facilitating the cross-talk between neurons, astrocytes, and microglia to promote physiological neuroprotective mechanisms that counteract neuronal cell death due to ischemic and excitotoxicity insults (Rosito et al., 2014).

Various studies have shown the importance of cell-cell interaction in the CNS. For instance, Park et al. reported that glial cells co-cultured with neurons having a mitochondrial thiamine deficiency, maintained neurońs neurite outgrowth, and cell metabolism (Park et al., 2001). This neuroprotective effect was linked to a reduction in oxidative stress and inflammation (Park et al., 2001). Besides, there is also evidence showing that production of the tumor necrosis factor alpha (TNFα) by microglial cells increases the expression of antioxidant enzymes that favors neuronal protection against excitotoxicity insults and ischemic brain injury (Bruce et al., 1996). Also, the response of astrocytes to microglial activation can also stimulate neuronal survival (Hailer et al., 2001). Other recent findings indicate that after brain trauma, male mouse astrocytes can transform to a neuroprotective phenotype mediated by microglia-derived cytokines and the downregulation of P2Y1 receptors (Shinozaki et al., 2017). However, not only the interaction of astrocytes with microglia has beneficial effects on brain tissue, but also astrocytes by activating and regulating the purinergic receptors P2Y1 and P2Y2 regulate calcium signaling and synaptic transmission and plasticity thus having potential therapeutic value for cognitive dysfunction (Fam et al., 2000; Gallagher and Salter, 2003; Guzman and Gerevich, 2016). In addition, the maintenance of cellular homeostasis and calcium signaling promotes cell survival in injured brain tissue (Bindocci et al., 2017; Khakh and McCarthy, 2015; Shigetomi et al., 2013a). Cell-cell interactions are essential for the maintenance of cognitive and motor functions in response to adverse conditions (Guzman and Gerevich, 2016).

New cellular studies have permitted to have a preliminary idea of the potential response of each type of cell to toxic or damaging insults and gave insights for possible therapeutic alternatives. In the following sections, the importance of astrocytes response to brain insults and the effect of SERMs on the maintenance of astrocytes' functions are reviewed.

3. Astrocytes are involved in CNS lesions and pathologies

Astrocytes are the most abundant in the CNS, which under normal conditions fulfill essential functions for the physiology of the system. Their primary functions are providing nutrients, recycling neurotransmitters and maintaining homeostasis (Pekny and Pekna, 2014; Sofroniew and Vinters, 2010) (Table 1). Also, the proximity of the endfeet of astrocytes with BBB (Chodobski et al., 2011) allows the secretion of antioxidants, anti-inflammatory molecules, growth factors, neurotrophins (Cabezas et al., 2014) and neurotrophic factors helping to the maintenance of the BBB (Sheng et al., 2013). In this context, astrocytes have a protective role in defense of the CNS. Many beneficial effects of astrocytes have been reported (Fernandez-Fernandez et al., 2012). In this respect, for example, a study with female astrocytes indicate that are not only good at protecting against ROS, but also there is strong evidence demonstrating that astrocytes accumulate copper (Cu) and protect neurons from the toxicity of this metal (Dringen et al., 2013; Tiffany-Castiglioni et al., 2011). Other astrocytic functions include cerebral blood flow (CBF), and regulation in response to neuronal activation by means of synthesis of prostaglandin E_2 (PGE_2) (Howarth et al., 2017). However, the release of PGE_2 is dependent on several factors such as glutathione levels (Howarth et al., 2017), intracellular calcium and extracellular glutamate levels (Sheng et al., 2013).

Several studies have shown that astrocytes are involved in different pathologies and lesions of the CNS (Cerciat et al., 2010; Pekny and Pekna, 2014). Astrocytes modulate the immune reaction, inflammatory proteins activity, and the formation of the glial scar and neuronal function (Sheng et al., 2013) and also these cells experiment changes in protein expression induced by stress (Burda et al., 2016). When these cells are subjected to mechanical lesions, an activation of ionic or cationic channels sensitive to the stretching of the cell membrane occurs. In astrocytes, stretching induces the influx of extracellular calcium, and sodium (Di et al., 2000; Ostrow et al., 2011), and metabolic and morphological changes, globally known as reactive astrogliosis. Astrogliosis is considered at the same time a detrimental and beneficial process. It may be detrimental to the recovery of neuronal function in pathologies of the CNS, such as PD (Dickson, 2012), multiple sclerosis (MS) (Nair et al., 2008), AD (Beach et al., 1989), TBI, and stroke (Derugin et al., 2000), as well as other pathologies that induce astrocytic hypertrophy and proliferation (Bagheri et al., 2013). Reactive astrogliosis stimulates the expression of the glial marker proteins such as the glial fibrillary acid protein (GFAP) and vimentin (Lin and Cai, 2004). These proteins are part of the intermediate filaments, and are concentrated in the cytoskeleton of astrocytes, where they play an essential role in the formation of the glial scar (Céspedes et al., 2013). The scar is a woven mesh between the processes of astrocytes surrounding the site of the lesion joined by tight and gap junctions (Lin and Cai, 2004). The glial scar is essential to seal the lesion and stimulates tissue remodeling mechanisms (Huang et al., 2014). Thus, astrogliosis can be considered as a defense response of the brain against the onset of an injury. Nevertheless, when this response is extensive, it generates adverse effects triggering high production levels of inhibitory molecules that suppress neuronal elongation and form powerful barriers to axon regeneration (van Niekerk et al., 2016).

As stated above, various neurodegenerative diseases, such as PD, are linked to astrogliosis. According to Brück *et al.*, there are α-synuclein (α-SYN)-dependent alterations of glial function, which has an impact on neuronal vulnerability to toxic insults (Bruck et al., 2016). In PD, secretion of pro-inflammatory molecules such as IFN-γ and TNFα contributes to the maintenance of astrogliosis activation with deleterious effects on dopaminergic neurons (Barcia et al., 2011). Recent findings suggest that there may be an excessive accumulation of α-SYN in astrocytes, which may cause astrogliosis and microglia activation affecting basic functions of neurons and astrocytes (Gu et al., 2010). On the other hand, protein S100β can influence the reactive characteristics of the astrocytes. For example, S100β can enhance the synthesis of inducible nitric oxide synthase (iNOS) in astrocytes, thus contributing to the progression of infarction, DNA damage and cell death by increased production of nitric oxide and ROS (Yasuda et al., 2004). In contrast, Bianchi *et al.*, using chemical methods showed evidence suggesting that S100 proteins reduce the polymerization of GFAP by inhibiting the protein nucleation step and polymer growth, thus

Table 1
Studies showing the protective function of astrocytes in different *in vivo* and *in vitro* models.

Model	Main findings	References
Astrocyte Reactivity and Reactive Astrogliosis	Provide nutrients, recycling neurotransmitters and maintaining homeostasis	Pekny and Pekna (2014) and Sofroniew and Vinters (2010)
Parkinson's Disease	Development and maintenance of the BBB	Cabezas et al. (2014)
Middle Cerebral Artery Occlusion	Formation of the glial scar	Céspedes et al. (2013)
Alzheimer's disease and aging cerebrum	Formation of tight and gap junctions to seal off the lesion and remodeling	Derugin et al. (2000) and Ostrow et al. (2011)
Parkinson's disease and Oxidative Stress Model	Secretion of antioxidant, anti-inflammatory, growth factors, neurotrophins and neurotrophic factors	Cabezas et al. (2014) and Sheng et al. (2013)
Astrocyte Calcium Signaling and Imaging Calcium Microdomains	Protection against ROS	Dringen et al. (2013) and Tiffany-Castiglioni et al. (2011)
	Protect neurons from the toxicity induced by Cu	Dringen et al. (2013) and Tiffany-Castiglioni et al. (2011)
Ca^{2+} signals from the entire 3D structure of astrocyte	Cerebral Blood Flow (CBF) regulation	Howarth et al. (2017)

Table 2
Estrogenic compounds and their protective effects in the CNS.

Compound	Cell Type or Model	Effect	References
Estrogens	Neuron/Alzheimer's disease	– Excitability and synaptic plasticity	Mukai et al. (2010)
	Neuron	– Promotes survival	Arevalo et al. (2010)
	Neuron	– Regulates cell differentiation, homeostasis and development	Ascenzi et al. (2006)
	Astrocytes/Stab Wound Injury	– Decreases GFAP expression in astrocytes	Lopez Rodriguez et al. (2011)
	Astrocytes – Microglia	– Decreases vimentin-immunoreactive astrocytes and immunoreactive microglia	Barreto et al. (2007)
17β-Estradiol (E2)	Astrocytes – Neuron	– Regulator of gene expression – Induces neuronal survival – Decreases glial activation – Anti-inflammatory and antioxidant effects	Cipolla et al. (2009), DonCarlos et al. (2009), Harms et al. (2001) and Lopez Rodriguez et al. (2011)
Estradiol	Astrocytes/Stab Wound Injury	– Reduced vimentin-immunoreactive astrocytes and GFAP-positive astrocytes and regulated CB1 and CB2 Receptors	Lopez Rodriguez et al. (2011)
Estrone (E1)	Traumatic Brain Injury - Rats	– Activates ERK1/2 and BDNF pathways – Decreases ischemic secondary injury and cell death	Gatson et al. (2012)
Testosterone	Stab Wound Injury - Rats	– Reduces astrogliosis	Barreto et al. (2007)
	Astrocytes/Glucose Deprivation	– Protects mitochondrial function and regulates neuroglobin expression	Toro-Urrego et al. (2016)
Dihydrotestosterone	Stab Wound Injury - Rats	– Reduces astrogliosis	Barreto et al. (2007)
Isoflavone Daidzein	Obesity Model - Rats	– Increases SGZ cell proliferation and reduces hippocampal apoptosis and gliosis	Rivera et al. (2013)
Equol	PC12 neuronal cells/Hypoxia/ Reoxygenation Injury	– Induces neuroprotection by inhibiting the generation of ROS as a result of down-regulation of gp91(phox) and inhibition of Src phosphorylation	Yu et al. (2016)
Genistein	Astrocytes/Alzheimer's Disease	– Anti-inflammatory effects of estrogenic compounds may be mediated and activated by PPARs suppressing	Valles et al. (2010)
3alpha-OH-Tib and 3beta-OH-Tib	Oligodendrocyte and Normal Human Astrocytes	– Agonist activity on astrocytes through ERα and ERβ – Increased gene transcription	Guzman et al. (2007)
Tibolone	Astrocytes/Glucose Deprivation	– Protection by a mechanism involving ERβ and the upregulation of neuroglobin	Avila-Rodriguez et al. (2016)
	Astrocytes/Glucose Deprivation	– Decreases cell death – Reduces nuclear fragmentation – Attenuates Superoxide ion production – Improves mitochondrial membrane potential – Regulates cytoplasmic calcium concentration	Avila Rodriguez et al. (2014)
	Neuro/Ozone Exposure	– Prevents memory deficits – Protects effect against oxidative stress and the cholinergic system disruption	Pinto-Almazan et al. (2014)
	Neuro/Ozone Exposure	– Prevented neuronal death – Prevented increased levels of lipid peroxidation and protein oxidation	Pinto-Almazan et al. (2014)

preventing the elongation of the glial scar (Bianchi et al., 1994).

Taking into account the impact of brain diseases on the welfare of the population by inducing cognitive and motor effects (Feigin et al., 2010; Hyder et al., 2007; Mar et al., 2011), new therapeutic avenues such as the use of estrogens have been seen as strategies to decrease secondary lesions while keeping a controlled response to insults. Therefore, preventing the progression of the injury and favoring brain repair. In the following sections, it will be discussed the neuroprotective actions of tamoxifen and other SERMs in brain cells exposed to different toxic insults mimicking pathological conditions. Special emphasis will be put on the mechanism of action and the receptors involved in search of possible therapeutics for different brain pathologies.

4. Neuroprotective effects of estrogenic compounds on the CNS

For some time, the use of estrogens has been considered useful for the maintenance of brain functions, and for treating and preventing various diseases (Table 2). Estrogens encompasses all steroid hormones with effects not only on the reproductive system of females, but also on other non-reproductive tissues such as adipose, bone, cardiovascular and brain tissues (Cui et al., 2013; Lu and Herndon, 2017; Mauvais-Jarvis et al., 2013).

Recent studies in female and male mice have revealed that estrogens have effects on neuronal excitability and synaptic plasticity by activating the ERα/ERβ nuclear receptors (Mukai et al., 2010). Estradiol and estrogenic compounds potentiate the neuroprotective functions of glial cells through the control of edema and glutamate levels after brain injury (Arevalo et al., 2010). At the developmental level, estrogens also have effects on the morphology, differentiation and functional properties of neurons apparently mediated by the ERα receptor and brain-derived neurotrophic factor (BDNF) (Ascenzi et al., 2006; Bondesson et al., 2015; Lu and Herndon, 2017).

In addition to the known effects of estrogens, it has been found that 17β-estradiol (E2), estrone (E1) and estriol (E3) have significant benefits in the functional maintenance of the CNS (Kikuchi et al., 2000). For example, estradiol regulates the activity of the endocannabinoid system through CB1 and CB2 receptors in conditions of stab wound brain injury, resulting in a reduction of reactive astrogliosis (Lopez Rodriguez et al., 2011; Mukai et al., 2010). However, estrogens are not only associated to brain functions, but also they are implicated in the regulation of cellular metabolism through the activation of mechanisms mediated by the interaction with estrogen receptors (Chalvon-Demersay et al., 2017; Fuente-Martin et al., 2013) in tissues such as adipose and brain (Brown et al., 2010). Various studies revealed the important role played by the activation of ERs in regulating the CNS metabolism and energy balance. For example, in patients with AD, the concentration of extracellular glutamate has been found increased, whereas treatment with estradiol increased glutamate uptake in astrocytes derived from these patients, suggesting a protective effect of estradiol against glutamate excitotoxicity in this neurodegenerative disease (Arevalo et al., 2010; Barreto et al., 2009; Fuente-Martin et al., 2013). It has also been described that estrogens can control fat reserves and modulate the central sensitivity to leptin (Fam et al., 2007; Matyskova et al., 2010). Taking into account the above, several studies reveal the beneficial effects of E2 in the protection of the stability of the BBB, the brain tissue and the organism as a whole (Maggioli et al., 2016; Villa et al., 2016), including metabolic disorders caused by excessive food intake (Hargrave et al., 2016; Hsu and Kanoski, 2014), as well as other pathologies such as ischemia, where the permeability of the BBB is altered permitting the entry of proinflammatory mediators to the brain.

Several studies reveal that estrogens have anti-inflammatory properties both in the periphery and at the CNS level. This is in accordance with studies that have shown estrogenic compounds such as tibolone reduced oxidative damage and inflammation in microglia (Hidalgo-Lanussa et al., 2018) and preserved mitochondrial functionality and cell morphology in astrocytic cells subject to an insult with palmitic acid (Gonzalez-Giraldo et al., 2018) and others such as E2 is neuroprotective against excitotoxicity by increasing the expression of glutamate transporters GLAST and GLT-1 in astrocytes (Xu et al., 2011).

E1 and some isoflavones are other compounds that have been shown to be neuroprotective. E1 has a protective effect against TBI by stimulating prosurvival pathways such as the ERK1/2 and BDNF pathways, thus decreasing both the secondary lesion and the cell death induced by this type of injury (Gatson et al., 2012). Some flavonoids such as calycosin, isorhamnetin, luteolin, and genistein strongly stimulate the synthesis and secretion of neurotrophic factors, including nerve growth factor (NGF), glial-derived neurotrophic factor (GDNF) and BDNF (Karki et al., 2014a; Xu et al., 2013). Specifically, bioproducts like isoflavones, daidzein, and genistein also exhibit a protective effect on astrocytes. In a previous study, it was found that the isoflavone daidzein (50 mg/kg) has estrogenic properties by reducing apoptosis of cultured cells from male wistar rats for almost two weeks (Rivera et al., 2013). In an animal model of fat-rich diet, daidzein reversed the high-fat diet-associated enhanced immunohistochemical expression of caspase-3, FosB, GFAP, ionized calcium-binding adapter molecule 1 (Iba-1), and ERα, in the hippocampus, an effect that was more prominent in the dentate gyrus (Rivera et al., 2013). In addition to its effects on behavior, cognition, and neuronal growth. Equol, the main active metabolite of daidzein, confers neuroprotection against hypoxia/reoxygenation injury in PC12 cells by the inhibition of ROS generation (Yu et al., 2016). On the other hand, the phytoestrogen genistein has shown anti-inflammatory effects, suppressing a diverse array of inflammatory responses caused by Aβ in astrocytes in a primary culture that was linked to PPAR activation (Valles et al., 2010). Furthermore, genistein also decreased the formation of Aβ aggregates and increased astrogliosis in cellular and animal models of AD (Bagheri et al., 2012; Valles et al., 2010).

Recent research also suggests a protective effect of other sex steroid hormones such as testosterone and its metabolite dihydrotestosterone on the CNS. For example, it has been found that in male rats subjected to brain injury, sex steroids reduced astrogliosis (Barreto et al., 2007), and dihydrotestosterone also diminished reactive microglia as well (Barreto et al., 2007). A separate study revealed that testosterone protected astrocytes exposed to glucose deprivation through the regulation of neuroglobin expression and the protection of mitochondrial function (Toro-Urrego et al., 2016).

Altogether this evidence opens a broad range of possibilities of the use of steroid hormones and estrogenic and similar compoundssuch as STEARs and SERMs for the protection of brain function. In this respect, various reports suggest beneficial effects of tibolone, a drug considered as STEAR, by the virtue of its estrogenic activity (Gambacciani and Levancini, 2014; Sadarangani et al., 2005). It was recently reported that tibolone significantly reduces the effects of glucose deprivation such as cell death, nuclear fragmentation, changes in mitochondrial membrane potential, superoxide ion production, calcium homeostasis and morphology in the astrocyte cell T98G (Avila Rodriguez et al., 2014). The data from this study suggested that tibolone exerts its effects through ERβ and the upregulation of neuroglobin (Avila-Rodriguez et al., 2016). Although actual research on the effect of tibolone on CNS protection has been increasing, the mechanism by which tibolone exerts these effects is still poorly understood. However, some mechanisms started to be elucidated. For example, tibolone has a neuroprotective effect diminishing neuronal damage and memory dysfunction caused by chronic exposure to ozone in male rats, likely as a consequence of the activation of SOD expression and the enhancement of the cholinergic system in the CNS of these rats (Farfan-Garcia et al., 2014). Furthermore, tibolone induced a decrease of peroxidized lipids, protein oxidation and neuronal death in the hippocampus that paralleled the prevention of memory and motor dysfunction induced by exposure to ozone. This evidence suggests that tibolone can be a good candidate for the prevention of neurodegeneration induced by oxidative stress (Pinto-Almazan et al., 2014). Based on this new evidence, estrogenic STEARs compounds are being evaluated as novel therapeutic agents for the treatment or prevention of different neurological pathologies (Arevalo et al., 2010). SERMs, which are synthetic estrogenic compounds, have neuroprotective effects similar to estrogens by selectively modulating ERs (Acaz-Fonseca et al., 2014). Below it is discussed more detailed information related to their protective effect, mechanisms of action or signaling pathways involved in the preservation of the physiology of the CNS.

5. Selective Estrogen Receptor Modulators

In addition to the multiple benefits mentioned above regarding the use of estrogens for the treatment or prevention of different pathologies in the CNS, other studies have argued that the use of estrogens can have adverse side effects. The adverse effects on the use of estrogens include the appearance of mammary and renal tumors after prolonged treatment with estrogen related to the activation of ERα (Russo and Russo, 2006). This has been strongly supported by studies that report on the occurrence and survival of breast cancer in patients who have been treated with estrogens or who have received hormonal replacement therapy (Perkins et al., 2018; Tian et al., 2018; Yue et al., 2010). In this regard, it is believed that the mechanism of action involved in the proliferation of cancer cells can be through several hormonal signaling pathways that induce the proliferation of renal cancer cells (Czarnecka et al., 2016) or through the estrogen/estrone metabolism pathway (Yager, 2015), and epigenetic cell reprogramming for breast cancer (Trevino et al., 2015). In addition to the carcinogenic effects of estrogens, recent investigations in ovariectomized rats (OVX) showed that high dosage of estradiol affected learning and memory, which is probably also related to its pro-oxidative effects (Khodabandehloo et al., 2013), alteration of the metabolism of estrogens, increased free radicals causing DNA damage (Kelloff et al., 1992) and the suppression of the expression of the antioxidant protein calbindin D28K (Bhat and Epelboym, 2004).

The use of synthetic and natural compounds that have a similar effect to estrogens, without causing these deleterious side effects in other tissues, has recently being promoted. These compounds might be considered as SERMs, which have become an integral part of a potential strategy for the treatment of different diseases such as osteoporosis, breast cancer (Gambacciani and Levancini, 2014; Reddel et al., 1983) and CNS disorders like PD (Dluzen et al., 2001), dementia (Yaffe et al., 2005) and AD (O'neill et al., 2004). SERMs are synthetic compounds that interact with ERs as ligands and induce changes in the receptor (Xu et al., 2016). SERMs have a high binding affinity to the ERs. For instance, the ER has two subtypes, ERα and ERβ, each encoded by genes located on different chromosomes; for example, ERα is encoded by chromosome 6, while the ERβ on chromosome 14 (Zhao et al., 2005). The activity of SERMs is determined by the interaction with ERα and ERβ (Khan et al., 2015). In this regard, SERMs modulate the interaction of ERs with co-activators and co-repressors (Ascenzi et al., 2006), thus having both agonistic or antagonistic effects depending on the tissue (Khan et al., 2015; Pfaffl et al., 2001). Among the SERMs that have been already tested for therapy or prevention are raloxifene (Khan et al.,

Table 3
SERMs and the protective effect in the CNS.

SERMS	Protective Effect	References
Tamoxifen	– Promotes axonal outgrowth.	Tian et al. (2009)
	– Attenuates inflammatory-mediated damage.	
	– Inhibits hydrogen peroxide formation.	Moreira et al. (2005) and Zhang et al. (2007)
	– Reduces the extent of lipid peroxidation.	
	– Increases neuronal outgrowth of hippocampal neurons.	
	– Reduces reactive astrocytes after a stab wound brain injury.	Barreto et al. (2009)
	– Reduces the glial scar.	Franco Rodriguez et al. (2013) and Suuronen et al. (2005)
	– Promotes neuronal survival.	
	– Regulates inflammatory cytokines IL1, IL6 and IP10	
	– Attenuates microglia activation and inflammatory cytokines.	Barreto et al. (2014) and Blasko et al. (2009)
	– Induces neuroprotective effect by reducing infarct zone in MCAO.	Kimelberg et al. (2003)
	– Reduces infarct volume as a result of diminished F2–isoprostanes (IsoPs) and F4–neuroprostanes (NeuroPs).	
	– Inhibits neuronal nitric oxide synthase activity.	Osuka et al. (2001) and Renodon et al. (1997)
	– Reduces the formation of 4-hydroxynonenal (4-HNE), 8-hydroxyl-2′-deoxyguanosine (8-OHdG) and the production of superoxide ion	Wakade et al. (2008) and Mosquera et al. (2014)
	– Attenuates pro-apoptotic proteins by increasing MnSOD	
	– Promotes neuronal survival	
	– Reduces nitrotyrosine levels along with inhibition of the formation of peroxynitrites.	Zhang et al. (2005)
	– Decreases myo-inositol (MI) associated with neurological disorders.	Ernst et al. (2002)
	– Improves the cholinergic system enhancing memory	Newhouse et al. (2013)
	– Increases the expression of GLT-1 and Transforming Growth Factor Alpha (TGF-α)	Feustel et al. (2004) and Lee et al. (2012b, 2009, 2008)
	– Reduces the levels of TNF-α and IL-1β.	Ismailoglu et al. (2010) and Mitra et al. (2015)
	– Decreases myelin loss.	
Raloxifene	– Increases neuronal outgrowth of hippocampal neurons.	O'neill et al. (2004)
	– Increases neurotrophic factors, anti-apoptotic molecules and protection of dopaminergic neurons.	Bourque et al. (2014)
	– Improves the expression of astrocytic transporters such as GLT-1 and GLAST.	Karki et al. (2014c)
	– Increases the expression of calcium memory-associated protein.	Zhou et al. (2015)
	– Favors neuronal survival against inhibition of calcium oscillation by high glutamate concentration.	
	– Beneficial effects on verbal memory and executive function.	Huerta-Ramos et al. (2014), Weickert et al. (2015) and Yaffe et al. (2005)
	– Beneficial effects on cognition.	
	– Decreases inflammation by inhibiting CCL20 and NF-κB in reactive astrocytes.	Li et al. (2014)
	– Inhibits proliferation of proteolipid peptide-related CD^{4+} T cells which are associated with autoimmune demyelination.	Bebo et al. (2009), Elloso et al. (2005) and Lei et al. (2003)
	– Decreases GFAP expression in astrocytes and Mac-1 in microglia.	
Raloxifene and Tamoxifen	– Inhibitory actions on TRPA1, TRPM2, and TRPV1 in hippocampal and dorsal root ganglion neurons.	Yazgan and Naziroglu (2016)
	– Diminish mitochondrial oxidative stress.	
	– Reduce caspase activation and apoptotic pathways	
	– Preserve neurogenesis and spine density.	Chakraborti et al. (2012), Khan et al. (2015) and Sanders et al. (2012)
	– Important for the synaptic function related to the learning process and long-term memory.	
Tamoxifen/4-Hydroxytamoxifen	– Induce neuroprotection against β-amyloid and glutamate.	O'neill et al. (2004)
	– Decrease ROS production	Kuo et al. (2003) and Mosquera et al. (2014)
	– Improve recovery of locomotor function	
	– Protect camptothecin-induced neuronal cell death through TGF-β	Dhandapani et al. (2005)
	– Reduce leukocyte infiltration and apoptosis at the site of the lesion.	Colon et al. (2016)
	– Increase the number of neurons.	
	– Decrease axonal degeneration.	
	– Decrease astrogliosis and GFAP immunoreactive cells.	
	– Reduce the induction of major histocompatibility complex II (MHC II).	Bebo et al. (2009)
	– Suppress the proliferation of myelin-specific CD^{4+} T cells.	
	– Inhibit T-helper type 1 differentiation (Th1) and T2 helper (Th2) by suppression of IFN-γ, TNF-α and IL12.	
	– Prevent weight loss at the brain level.	Feng et al. (2004)
	– Protective effect on mitochondrial function.	Moreira et al. (2005, 2004) and Saladores et al. (2015)
	– Reduce the production of hydrogen peroxide (H_2O_2).	
	– Attenuate lipid peroxidation.	
	– Protect the permeability of the calcium-induced mitochondrial transition pore (MPT).	

2015), tamoxifen (Gonzalez et al., 2016) and toremifene (Szamel et al., 1998), among others (Table 3). The use of these compounds for the treatment of various diseases or the protection of CNS against different lesions is discussed in the following sections.

5.1. Raloxifene

Raloxifene is a second generation SERMs and is derived from benzothiophene (Abdelhamid et al., 2011; O'neill et al., 2004). The metabolism of this compound is not mediated by the cytochrome P450 pathway but occurs through glucuronidation (Heringa, 2003; Kemp et al., 2002). This metabolism is carried out by the hepatic UDP-glucuronosyltransferases (UGT) 1A and 1A9, and for this reason, patients treated with this compound have high levels of glucuronides and only 1% of raloxifene in plasma (D. Sun et al., 2013). These UGT are well expressed in astrocytes and endothelial cells, but neurons have lower expression (Gradinaru et al., 2012; Suleman et al., 1998). Raloxifene has shown beneficial effects against neurotoxicity and inflammation in neurodegenerative disorders, autoimmune diseases and stroke.

A protective effect of raloxifene on dopaminergic neurons subjected to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is noted. This protective effect was mediated by the simultaneous activation of the G protein-coupled estrogen receptor 1 (GPER1) and the Akt signaling striatal pathway with the increase in Bcl-2 and BDNF, but no significant activation of the extracellular signal-regulated kinase-1 (ERK) 1/2 signaling (Bourque et al., 2014). In another study performed in rat cerebral cortex, raloxifene was found to increase glutamate uptake and GLT-1 protein and mRNA expression, under high levels of manganese (Mn) (Karki et al., 2014c). These changes in gene expression were mediated by several signaling pathways such as ERK, EGFR, and CREB through ERα, ERβ, and GPR30. Moreover, the treatment with raloxifene regulated the expression of GLAST by activating NF-κB through the ER (Karki et al., 2014c).

Glutamate has several functions within the CNS, including the regulation of intracellular calcium waves (Ca^{2+}) associated with learning and memory processes (Pasti et al., 1995). According to a previous study, glutamate regulated calcium oscillations and protein expression associated with calcium levels in a concentration-dependent manner but observed that after raloxifene treatment neuronal survival increased (Suuronen et al., 2005). This effect correlated with a 33% decrease in cognitive deterioration after treatment with raloxifene (Legault et al., 2009). Likewise, studies on transient receptor potential (TRP) cation channel family members that are activated by oxidative stress such as TRPA1, TRP melastatin 2 (TRPM2), and TRP vanilloid 1 (TRPV1) showed an increase in cytosolic calcium levels with subsequent neuronal toxicity, ROS increase, and cell death in ovariectomized rats (OVX) (Yazgan and Naziroglu, 2016). These deleterious effects were diminished considerably after treatment with raloxifene and other estrogenic compounds through the regulation of anti-apoptotic pathways including caspase-3 and caspase-9 (Yazgan and Naziroglu, 2016). The evidence discussed above has left open the possibility that raloxifene can be used as a drug to improve the expression of glutamate transporters or other channels that present alterations in various neurodegenerative diseases such as AD in women after menopause.

Several studies have shown that the use of estrogenic compounds improves learning and memory. A previous study showed that in addition to being used as a hormone replacement therapy, raloxifene also has beneficial effects on cognition (Huerta-Ramos et al., 2014). For example, a study conducted in postmenopausal women using functional magnetic resonance imaging (fMRI) revealed an effect on memory and visual brain activation patterns in women treated with raloxifene (60 mg) compared to the controls (Neele et al., 2001). Another study in which raloxifene was used as a complementary therapy for schizophrenia reports evidence suggesting an improvement of cognitive abilities such as verbal memory and attention in men and women treated with raloxifene (120 mg/day) when compared to controls (Abdelhamid et al., 2011; Szamel et al., 1998). However, the use of estrogens as adjuvant therapy in the treatment of schizophrenia in both men and women is not under use because of their unwanted side effects and more importantly the variable therapeutic results that have been reported. For example, a different study showed no improvement in cognitive function, nor recovery of memory or verbal attention in postmenopausal women treated with raloxifene (60–120 mg/day) (Ditkoff et al., 1991; Kemp et al., 2002; Polo-Kantola et al., 1998; Shaywitz et al., 1999). Therefore, it is necessary to delve more into the mechanism of action of raloxifene and other estrogenic compounds to find new therapeutic targets toimprove cognitive functions in patients with schizophrenia and neurodegenerative diseases.

Raloxifene has anti-inflammatory effects (Li et al., 2014) that were linked to the inhibition of CCL20, which promotes Th17 cell migration and also suppresses IL-1β-induced NF-κB activation (phosphorylation of p65) in reactive astrocytes (Li et al., 2014). In agreement with an anti-inflammatory action, raloxifene has a positive effect on MS, a disease characterized by chronic inflammation (Bebo et al., 2009). Also, it has been shown that raloxifene also affects the proteolipid peptide-related T cells ($CD4^{+}$) (Elloso et al., 2005), which play an important role in autoimmune demyelination (Fletcher et al., 2010), and decreased expression of GFAP in astrocytes, and Mac-1 in the microglia in the dentate gyrus and CA1 region of the hippocampus after treatment with raloxifene (Lei et al., 2003). These findings leave open the possibility that raloxifene can influence glial-mediated inflammatory pathways and possibly protect against inflammatory and autoimmune diseases.

Raloxifene has shown to preserve neurogenesis and the density of the spine in the cerebral cortex after the transitory occlusion of the middle cerebral artery (MCAO) in female rats neurons (Khan et al., 2015). Also, it has been reported that in male rodents, hippocampal pyramidal neurons treated with tamoxifen and raloxifene showed increased density of dendritic spines and changes in geometry, probably mediated through the increase in BDNF (Chakraborti et al., 2012; Gonzalez-Burgos et al., 2012; Sanders et al., 2012). Raloxifene can also be involved in brain plasticityand synaptic functions that are crucial for learning and memory processes. Hence, further studies are needed to address this issue, and the mechanism of action and signaling pathways involved, among others.

5.2. *Tamoxifen*

Tamoxifen is a derivative of triphenylethylene, a non-steroidal analog of estradiol (Neven et al., 2018) and a first-generation SERM, mostly known for its therapeutic use against breast cancer (Chang et al., 2011; Peng et al., 2009). Nevertheless, several studies have also shown beneficial effects of tamoxifen in the brain (Barreto et al., 2009; Dhandapani and Brann, 2003). Tamoxifen has an affinity for the ER about 100 and 1000 times higher than estrogens. Recent findings suggest that tamoxifen crosses the BBB (Kimelberg et al., 2003; Lien et al., 1991) eliciting a response in the brain similar to estradiol (Galván-Ramírez et al., 2016). Tamoxifen is considered a molecule with an estrogen agonist profile (Barreto et al., 2009) and, like estradiol, reduced reactive astrocytes in the surroundings of a stab wound brain injury.

To date, several studies support the theory that tamoxifen has effects on the CNS (Franco Rodriguez et al., 2013; Moreira et al., 2005). The effect of tamoxifen on several brain pathologies has been evaluated including TBI, cerebral ischemia, cerebrovascular stroke, subarachnoid hemorrhage, and spinal cord injury. Also, alterations in the levels of excitatory amino acids and inflammation involved in neurodegenerative diseases, as well as inflammatory autoimmune disorders and infectious diseases. To some extent, the effect of tamoxifen on these diseases may be at least in part due to their protective effect on mitochondrial function (Moreira et al., 2005). In this regard, tamoxifen was found to reduce the production of hydrogen peroxide (H_2O_2), lipid peroxidation and oxidation of thiol groups and Glutathione (GSH) levels promoted by Ca^{2+} (Moreira et al., 2005).

Previous studies have reported different routes and mechanisms of action by which tamoxifen exerts its neuroprotective action on various diseases. Tamoxifen exerts a significant effect in reducing reactive male wistar rats astrocytes after brain injury (Franco Rodriguez et al., 2013). This reduction in the proliferation of astrocytes by tamoxifen may be mediated by the inhibition of the Protein Kinase C (PKC) involved in the proliferative signaling pathways (Horgan et al., 1986). This study also demonstrated a tamoxifen-induced decrease in vimentin, as well as the production of IL-1, IL-6, and IL-10, an effect that can be mediated by ERα and NF-κB promoting neuronal survival in this type of injury (Horgan et al., 1986).

5.2.1. *Neuroprotective effects of tamoxifen*

In hippocampal neurons, tamoxifen and 4-hydroxy-tamoxifen at low concentrations induced neuroprotection against Aβ and glutamate toxicity, two neurotoxins associated with AD (O'neill et al., 2004). Furthermore, previous reports show evidence that tamoxifen also affects the expression of glutamate transporters. For example, tamoxifen increased the expression of GLT-1, a glutamate transporter which expression is altered in AD and stroke (Lee et al., 2008), and decreased the excitotoxicity induced by chronic exposure to manganese (Lee et al., 2009). The increase in the expression of GLT-1 has been reported to be mediated by the transforming growth factor-α (TGF-α) (Lee et al., 2012b, 2008). In the same study, knockdown of TGF-α using siRNA abolished the E2/TX effect on GLT-1 expression, and also the use of tamoxifen increased the protein and mRNA levels of TGF-α. This finding is of great importance because TGF-α is considered as neurotrophic and neuroprotective (Karki et al., 2017; Lee et al., 2009; Yuen and Mobley, 1996).

In addition to the above benefits, the effect of tamoxifen has also been tested *in vivo* models of different brain pathologies. For example, tamoxifen (20 mg/kg) reduced the infarct zone after 3 h, likely due to its ability to inhibit the release of excitatory amino acid and lipid peroxidation (Kimelberg et al., 2003; Zhang et al., 2007), possibly as a result of a decrease in F2-isoprostanes (IsoPs) and F4-neuroprostanes (NeuroPs), and biomarkers of oxidative damage (Montine et al., 2002) or the inhibition of the neuronal NOS(nNOS) (Renodon et al., 1997). Tamoxifen has been also demonstrated to exhibit an inhibitory role in the formation of citrulline mediated by the binding of calmodulin and nNOS (Ohashi et al., 2007). It is important to highlight that tamoxifen in reversible occlusion models of the middle cerebral artery (rMCAO) decreased excitatory amino acid in penumbra areas by acting on the volume-regulated anion channels (VRACs), an effect considered even more relevant than the reversal of GLT-1 (Feustel et al., 2004). Likewise, in a rat model of rMCAO, tamoxifen was considered as an inhibitor of Ca^{2+}/Calmodulin-dependent NOS activity (Osuka et al., 2001). Indeed, tamoxifen reduced the formation and production of 4-hydroxynonenal (4-HNE), 8-hydroxyl-2′-deoxyguanosine (8-OHdG) and superoxide ion, attenuated pro-apoptotic proteins in ischemic female rats through an antioxidant mechanism that involves the increase in MnSOD expression and attenuated ERK signal favoring neuronal survival in ischemic nucleus at 24 h post-injury (Wakade et al., 2008). Furthermore, tamoxifen significantly attenuated nitrotyrosine levels along with inhibiting the formation of peroxynitrites in proteins (Zhang et al., 2005) and this may be one mechanism responsible for its neuroprotective effect on ischemic injury models.

Tamoxifen has shown neuroprotective effects in the context of biochemical events associated with the secondary lesion framed in a male rat model of spinal cord injury. This neuroprotection is accompanied by the reduction of TNFα levels and IL-1β and ultrastructural changes after 6 h (Ismailoglu et al., 2010), reduction of ROS production with treatment by tamoxifen 30 min post-injury (Tian et al., 2009) or improvement in recovery in motor function 21–28 days post-injury (Mosquera et al., 2014). Altogether, these data suggest tamoxifen as a therapeutic alternative for the treatment of spinal cord injury in chronic stages. Previous studies also support the neuroprotective and restorative role of tamoxifen through an antioxidant mechanism that reduces the production of superoxide and oxidative damage in the penumbra of the cerebral cortex, in addition to decreasing the activation of caspase-3 (Ismailoglu et al., 2010). Furthermore, tamoxifen also exerts neuroprotective actions in animal models of ischemia. For example, tamoxifen was found to be neuroprotective in a rat model of permanent MCA occlusion, considered to be a realistic model of human stroke. In this case, tamoxifen induces neuroprotection when it is administered within 3 h of the occlusion attenuating the increase in excitatory amino acids (Kimelberg et al., 2003). In canine models, tamoxifen was reported as effective in reducing the neurological deficits and the size of the infarct area in the brain of male beagles after ischemia (Boulos et al., 2011). Meanwhile, other studies reported that tamoxifen accumulated in the brain over long periods due to its ability to cross the BBB (Li et al., 2012). In this concern, tamoxifen has effects on the tissues by causing marked inhibition in the protein expression of the Toll-like Receptor Type 4 (TLR4), NF-κB and downstream molecules such as IL-1β, TNF-α, IL-6 and the intercellular adhesion molecule-1 (ICAM-1) (X. Sun et al., 2013). This effect of tamoxifen not only improved early brain injury (EBI), but also had beneficial effects on cerebral edema, BBB impairment, and clinical behavior scale, with a direct impact on learning and memory in adult male rats with subarachnoid hemorrhage (SAH) (X. Sun et al., 2013). Also tamoxifen prevented brain weight loss and at low concentrations blocked 3-nitropropionic acid-induced intracellular Ca^{2+} increase and cell damage (Feng et al., 2004). However, many studies reported that high concentrations of tamoxifen can also induce cell damage after hypoxic-ischemic brain injury in male and female rat pups, but this damage is much lower in adult female rats (Feng et al., 2004).

Finally, studies in elderly women confirmed that tamoxifen affects brain homeostasis, in a similar form of that from estradiol. Using proton magnetic resonance spectroscopy, it was found that women treated with tamoxifen or estrogen had lower concentrations of myo-inositol (MI) in the brain in comparison to controls (Ernst et al., 2002). Since changes in myo-inositol have been associated with neurological conditions such as AD (Voevodskaya et al., 2016) and brain injury, suggesting that these changes can be of clinical relevance (Kierans et al., 2014).

5.2.2. *Tamoxifen, memory and neuroinflammation*

Previous studies also indicated that tamoxifen improves the cholinergic system function and, as a consequence, the hippocampal-dependent learning and memory processes in postmenopausal women (Newhouse et al., 2013). Similarly, other studies have shown a clear relationship between tamoxifen and improvement in learning and memory of ovariectomized rats (OVX), probably through its protective effects against oxidative damage of the brain (Zabihi et al., 2014). In fact, recent studies have reported that after intoxication by MPTP, the frontal cortex shows a neurodegeneration associated to glial cells and the activation of the canonical pathway of NFκB: IKK2-IκB-RelA:p50 and/or the non-canonical pathway that induces the nuclear translocation and transcriptional activity of the dimer NF-κB/RelB:p52. In one of these studies, they investigated the effect of estrogenic compounds (17-β estradiol, tamoxifen and 17-β estradiol + tamoxifen) over the progression of neurodegeneration and changes in the molecular and cellular pattern of NF-κB as p65, p52, RelB and NIK in the frontal cortex of Swiss male and female albino mice treated with MPTP. They found that the activation of these pathways depend on the function of estrogens through their nuclear or cytosolic ERs. They suggested that the variability of estrogen level and actions through ERs may explain that men are more prone to develop PD than women (Mitra et al., 2015).

Upon neuroinflammation, tamoxifen and raloxifene decrease the inflammatory response in both astrocytes and microglia submitted to lipolysaccharide (Arevalo et al., 2012). Similary, in other study, a reduction of microglia activation was also reported in ovariectomized rats. This response was found in cells after being treated with 17β-estradiol, raloxifene and tamoxifen after penetrating brain injury (Barreto et al., 2014; Blasko et al., 2009). Likewise, anti-apoptotic actions of these compounds by an ER-mediated mechanism were observed in microglial cells treated with LPS and different concentrations of tamoxifen and raloxifene (Suuronen et al., 2005). This mechanism was mediated by inhibitory signals affecting TGF-β (Perry et al., 1995) and heat-shock proteins such as HSP72 (Gabai et al., 2000), which are responsible for the transient activation of MAPKs such as p38 and ERK1/2. However, defining the anti-inflammatory signaling pathway induced by SERMs in microglial cells requires further studies.

A protective effect of tamoxifen has been observed in MS and hypoxic-ischemic brain injury. In MS, it has been demonstrated that it suppresses myelin-specific CD^{4+} T-cell proliferation, apparently through a mechanism that involves the downregulation of MHCII levels in the plasma membrane or the induction of TGF-β, a cytokine with known anti-proliferative effects on T-cells. The authors also report an inhibition of the differentiation of Th1 and Th2 (Bebo et al., 2009), which may be related to tamoxifen's ability to inhibit the production of IL-12, as the main cytokine responsible for the generation of inflammatory Th1 cells (Komi and Lassila, 2000; Liu et al., 2002). For this reason, tamoxifen can be considered as a regulator of the immune response that may be potential for the treatment of inflammatory autoimmune disorders affecting the CNS. In this regard, tamoxifen improves the outcome by attenuating symptoms of encephalomyelitis and degree of demyelination in an experimental autoimmune encephalomyelitis model performed on adult female mice (Bebo et al., 2009). Otherwise, a study with six-week-old male and female mice found the co-administration of tamoxifen and 17β-estradiol attenuates the damage in *in vitro* astrocytes infected with the toxoplasma Tachyzoite (Galván-Ramírez et al., 2016) through the inhibition of the ER, which has an important effect in reducing parasite proliferation (Dittmar et al., 2016).

The possible mechanisms by which tamoxifen might have a neuroprotective effect have been increasingly described by different investigations as we have previously shown. Its beneficial effect on the maintenance of brain function has been demonstrated *in vivo* as well as *in vitro*, and represent a possible alternative for the treatment of various brain pathologies. This also guarantees the safety of this compound in the treatment of cancer, but it is necessary to apply and specify the mechanisms of action in some pathologies, as well as to identify more precise aspects related to its metabolism and elimination.

5.2.3. *Active metabolites of tamoxifen*

Tamoxifen is transformed in the liver into three active metabolites, *N*-desmethyl-4-hydroxytamoxifen (Endoxifen), α-hydroxytamoxifen, and 4- and 3-hydroxytamoxifen, which are metabolized by the cytochrome P450 enzyme complex (Cyps) (Table 4). For instance, the P450 (Cyps) is a family of proteins characterized by their ability metabolizing drugs and xenobiotics compounds (Meyer et al., 2001). Although Cyps enzymes are found in a smaller amount in the brain than liver, the knowledge of metabolism of several drugs by these enzymes has now been well established. As for tamoxifen metabolites, the 4-hydroxy Tamoxifen has an affinity for ER one hundred times greater than tamoxifen. However, it only constitutes about 10% of its primary oxidation. On the other hand, endoxyphene is the most active metabolite, and it has similar characteristics at high concentrations (Irarrazaval, 2011).

CYP enzymes have a beneficial effect on the brain (Miksys et al., 2000) and are expressed in astrocytes (Gambaro et al., 2016) and neurons (Nebert et al., 2013). Currently, some isoforms of CYP450 have been described with a neuroprotective effect in the brain (Terashvili et al., 2012). CYP2E1 responds to inflammatory factors such as lipopolysaccharides and IL-1β, increasing its expression in rat glial cultures in the face of an ischemic lesion (Tindberg et al., 1996). CYP2C29 prevents the cytotoxic effect in the brain by metabolizing phenytoin at high concentrations (Meyer et al., 2001). It has also been reported to promote cell proliferation, tube formation and migration in human retinal astrocytes after hypoxia (Capozzi et al., 2014). The abuse of cocaine consumption reduces the regulation of CYP2C8 and CYP2C9 genes, which play an important role in the modulation of cerebrovascular functions, thus increasing the risk of cardiovascular diseases (Malaplate-Armand et al., 2005). CYP3A is expressed in astrocytes (Naud et al., 2016) and is related with the metabolism of psychoactive drugs (Woodland et al., 2008) and steroid hormones that are involved mainly in the early development of the brain (Krauser and Guengerich, 2005; Rosenbrock et al., 1999). Similarly, CYP2D6 is an enzyme expressed in the brain that metabolizes drugs and endogenous neuronal compounds (Mann et al., 2012). Also, CYP2D6 has been able to reduce neuronal cell death by reducing the neurotoxic effect in neurons (Mann and Tyndale, 2010). CYP2D6, which is also present in the mitochondrial membrane of neurons, is involved in the metabolism of several drugs related to AD and PD (Mann and Tyndale, 2010; Miksys et al., 2002). On the other hand, CYP2B6 and CYP2B1 are highly expressed in BBB (Dauchy et al., 2008). The increased CYP2B6 expression level in neurons and astrocytes is related to smoking and alcohol intake, which increased the risk of development of neuropathologies and cancer (Miksys et al., 2003). In male rat brains, nicotine exposure increased the levels of CYP2B1 triggering the rise of carcinogenic metabolites, susceptibility to mutagenesis, genotoxicity, and cell death (Miksys et al., 2000). CYP450 enzymes have been characterized in the brain and it has been discover that some isoforms are expressed mainly in the endoplasmic reticulum and mitochondria of astrocytes and neurons (Lavandera et al., 2015).

Some CYPs are involved in the metabolism of several drugs (Bajpai et al., 2013). CYP2D6, CYP2C9 and CYP3A are the primary enzymes that convert tamoxifen into different active metabolites (Singh et al., 2011). Tamoxifen has been used as a treatment in different brain lesions and pathologies, while its substrate and its signaling mechanism in the brain are not clear, there is evidence of the action and metabolism of these enzymes in the liver. For example, the bioactivation of tamoxifen in breast cancer is carried out by several isoforms of CYP in the liver, which is metabolized through different reactions such as N-demethylation, 4-hydroxylation, α-hydroxylation and N-oxidation (Desta et al., 2004). The N-demethylation reactions of tamoxifen are catalyzed by the enzymes CYP3A, CYP3A4, and CYP3A5 and produce N-demethyltamoxyphene (DMT) (Reddel et al., 1983; Wegman et al., 2007; White, 2003). The α-hydroxytamoxifen is catalyzed by CYP3A4 in liver (Boocock et al., 1999), but the family of CYP3A is widely expressed in brain and have an important role in steroid metabolism (Woodland et al., 2008). The 4- and 3-hydroxy-TAM are catalyzed by CYP2B6, CYP2C19 and CYP3A5 (Dehal and Kupfer, 1999; Jordan, 2007; White, 2003). The *N*-desmethyl-4-hydroxytamoxifen (Endoxifen) is catalyzed by CYP2D6 and CYP3A (Ahmad et al., 2010; Teft et al., 2011).

Considering the discussion above, tamoxifen can be metabolized by the CYP450 enzymes in the brain by crossing the BBB, but the mechanism involved restricts the accumulation of tamoxifen in the brain and its metabolites. Also plays an important role the Glycoprotein P(P-gp), which is an ATP-dependent drug/flow pump expressed in endothelial cells that acts as a transporter in the BBB limiting the cerebral penetration of drugs (Dauchy et al., 2008). For example, one study

Table 4

Degradation and metabolites of raloxifene and tamoxifen in brain tissue and other tissues.

SERMs	Enzyme (s)	Function (s)	Metabolite (s)	Cell-type	References
Raloxifene	UDP-glucuronosyl-transferases (UGTs) UGT1A1	Metabolism of endogenous compounds (bilirubin, steroid hormones, bile acids, fatty acids) and detoxication of drugs and xenobiotics, besides the regulation of neurotransmitters (Dopamine and serotonin).	Raloxifene-4′-Glucuronide Raloxifene-6-Glucuronide	Astrocytes Endothelial Cells Neurons	Dluzen et al. (2014), Gradinaru et al. (2012), Kemp et al. (2002), Ouzzine et al. (2014), Suleman et al. (1998) and D. Sun et al. (2013)
Tamoxifen	P450 (CYPs) enzymes CYP2D6, CYP2C9 and CYP3A	Proteins characterized for their ability of metabolize drugs and xenobiotics compounds. Moreover, the CYPs have exhibited a neuroprotective effect in brain against injuries, pathologies and by inactivating neurotoxins.	*N*-desmethyl-4-hydroxytamoxifen (Endoxifen) α-hydroxytamoxifen 4-hydroxy-tamoxifen 3-hydroxy-tamoxifen	Astrocytes Endothelial Cells Neurons	Gambaro et al. (2016), Malaplate-Armand et al. (2005), Mann et al. (2012), Meyer et al. (2001), Singh et al. (2011) and White (2003)

showed that in the absence of P-gp, tamoxifen and its metabolites increased its accumulation slightly, whereas the activation of P-gp by tamoxifen decreased its accumulation (Iusuf et al., 2011). Likewise, a study evaluated the time of total degradation of tamoxifen and its metabolites such as 4-Hydroxytamoxifen, N-desmethyl-tamoxifen, endoxifen and norendoxifen in the CNS, and found that the degradation of tamoxifen, and its metabolites, take up to 8 days depending on factors such as mouse strains, age, and dosage (Valny et al., 2016). Understanding these aspects is fundamental for the treatment with tamoxifen since the effectiveness of the treatment depends on the concentration of the drug.

5.2.3.1. 4-Hydroxytamoxifen. 4-Hydroxytamoxifen the active metabolite of tamoxifen, has 25 to 50 times higher binding affinity than tamoxifen for the ERs (Fabian et al., 1981). Even though 4-hydroxytamoxifen has a higher affinity for ERs, other studies showed relative binding affinities in percentage to be 36% for ERα and 43% for ERβ compared to 100% for 17β-estradiol (Qiu et al., 2003). The above finding indicates that 4-hydroxytamoxifen has not an estrogenic activity similar to that of tamoxifen. In another study, it was shown evidence that 4-hydroxytamoxifen prevented the loss of cytochrome *C* induced by calcium, exhibiting high antioxidant capacity (Moreira et al., 2005). Indeed, tamoxifen and 4-hydroxytamoxifen had similar protectives effects in response to increased levels of TGF, inducing the release of anti-inflammatory cytokines with neuroprotective properties in cortical astrocytes (Dhandapani et al., 2005). Similarly, tamoxifen and 4-hydroxytamoxifen increased neuronal survival against toxic insults such as Aβ and glutamate-induced toxicity, both linked to neuronal degeneration in AD (O'neill et al., 2004). In the same study, it was mentioned that both compounds did not affect the neuronal process (Yazgan and Naziroglu, 2016), outgrowth and memory function in the complexity of cortical, hippocampal, or basal forebrain (O'neill et al., 2004). In contrast, in adult male Sprague–Dawley rats tamoxifen has been shown to promote axonal growth and clearly reduced the number of apoptotic neurons after spinal cord injury by reducing the production of axonal growth inhibitors, as well as significantly attenuating the production of IL-β induced by microglial activation (Tian et al., 2009). This confirms that tamoxifen provides neuroprotective effects and may have a therapeutic potential on human spinal cord injury.

Other studies have shown that 4-hydroxytamoxifen prevents mitochondrial dysfunction and inhibits lipid peroxidation caused by the ADP/Fe^{2+} oxidant pair, as well as the mitochondrial permeability of the transition pore, decreasing the level of repolarization and an increase in the repolarization phase (Moreira et al., 2004). 4-Hydroxytamoxifen also shows a protective effect against oxidative stress by eliminating free radicals such as the superoxide ion by inducing the expression of MnSOD (Kuo et al., 2003; Pinto-Basto et al., 2009). 4-Hydroxytamoxifen is an active signal transducer that stimulates the activator of transcription 3 (STAT3) inhibiting the differentiation of stem cells by binding to ERs (Matsuda et al., 1999).

6. Molecular mechanisms of the SERMs dependent on the action of Estrogen Receptors

Tamoxifen and its active metabolites compete with estrogens for binding to ER. The genomic effects of tamoxifen are related to the activation of ERα and ERβ inducing a different conformation of the ER to the conformation induced by 17β-estradiol (E2) and other potent estrogens (Zhou et al., 2007) (Table 5). Tamoxifen is a potent activator of ER-mediated induction of promoters regulated by AP-1 sites that include the promoter of the human collagenase gene and constructs in which an AP-1 site is fused with the promoter of herpes thymidine kinase (Eberling et al., 2004; Miksys and Tyndale, 2004). Tamoxifen agonist at AP-1 sites is specific to the cell type and occurs in cell lines of uterine origin, but not of mammary origin and it is paralleled to tamoxifen agonist *in vivo*. AP-1 proteins such as Jun or Jun/Fos are necessary for stimulation with tamoxifen, since it increases the transcriptional efficiency even when they are provided in optimal amounts. In a previous study, 4-hydroxytamoxifen in astrocytes exhibited an agonist effect that binds to the reporter driven by ER-α and AP-1 (Guzman et al., 2005, 2007). Similarly, other studies showed that tamoxifen binds to ER and activates dielectric barrier discharge, which increases the transcriptional efficiency of Jun/Fos in AP-1 promotion sites (Webb et al., 1995), as well as both tamoxifen and raloxifene were found to be potent activators of ER-β and AP-1 mechanism through which gene transcription was triggered (Paech et al., 1997). In a previous study, it was also found that treatment with tamoxifen increased the levels of the phosphorylated forms of the Jun N-terminal kinases (JNK), c-Jun and AP-1 (Schiff et al., 2000). From the molecular point of view, it was also suggested that ERβ and ERα have different roles in gene regulation and response according to the ligand, and that the regulation of tamoxifen and raloxifene differed in different brain regions (Eberling et al., 2004; Zhou et al., 2002). For example, one study showed that tamoxifen increased the levels of ERβ mRNA in the hypothalamus, but raloxifene augmented levels of ERβ mRNA in the amygdala, while another study suggested that tamoxifen stimulated ERβ, triggering the transcription of the AP-1 complex in hippocampal cells (Pak et al., 2005).

Tamoxifen, raloxifene, ospemifene and bazedoxifene exhibited a similar response to that of estradiol on inflammation. These SERMs decreased IL-6 and IL-10 expression under lipopolysaccharide (LPS) insult in astrocytes. Regarding ospemifene and bazedoxifene, it was observed that these compounds inhibit the nuclear translocation of the p65 subunit of NF-κB induced by LPS though an ER-dependent mechanism (Cerciat et al., 2010). In an spinal cord injury model, tamoxifen reduced NF-κBp65, and activation of phosphorylated IκBα and caspase 3 (Wei and Ma, 2014), suggesting that this compound is an inhibitor of the IKKB/NF-κB pathway. Similarly, raloxifene triggers an anti-inflammatory process through ER by blocking the translocation of NF-κB p65 to the nucleus, reducing the expression of IL-1β and TNF-α and its suppressive effect on the expression of CCL20, which activates the migration of Th7 by astrocytes in an experimental model of autoimmune encephalomyelitis (Li et al., 2014). Among other studies, tamoxifen activated PI3K through an ER-mediated mechanism, which, in turn, induced the inhibition of inflammatory gene transcription, the transport of NF-κB to the nucleus and reduced astrogliosis, as well as decreased the number of proliferating NG2 cells acting on ER (Franco Rodriguez et al., 2013). Furthermore, in glioblastoma cells, it was observed that activation of ERα-36, a variant of ERα, has shown an action similar to that of tamoxifen, showing a neuroprotective effect that involves MAPK/ERK and PI3K/Akt (Liu et al., 2016). Indeed, low concentrations of tamoxifen increased the expression of ERα-36 in hippocampal neurons following MCAO (Zou et al., 2015).

Tamoxifen contributes to reducing the excitotoxicity in astrocytes since it binds to ER and increases the expression of transforming growth factor (TGF) and GLT1 (Lee et al., 2012b). In neurodegenerative diseases such as PD, whereby toxicity is produced by an increase in the concentration of manganese in astrocytes, thus inducing oxidative stress, energetic alterations and loss of mitochondrial potential. In this regard, treatment with tamoxifen (1 μM) reduced the toxicity by attenuating ROS production through mechanisms not dependent on ER and probably because of its antioxidant properties (Milatovic et al., 2007) and activation of PI3K/Akt (Yu et al., 2004). Another study reported that tamoxifen also decreased cell death in astrocytes isolated from cerebral cortex of newly born Sprague-Dawley rats by activating PI3K/Akt and MAPK/ERK signaling pathways after 24 h of manganese insult (Lee et al., 2009). Taken together these findings, tamoxifen exhibited an effective therapeutic actions against manganese toxicity, which is found increased in some neurodegenerative diseases. Several other experiments have reported that tamoxifen improves the astroglial uptake of glutamate via glutamate-aspartate transporter (GLAST) in rat

Table 5
Classic receptors: Estrogen Receptors alpha and beta activation by SERMs.

SERM	Receptor	Main Findings	References
Tamoxifen	ERβ mRNA levels	– Increased in hypothalamus.	Zhou et al. (2002)
	ERβ	– Increased phosphorylated JNK c-Jun.	Schiff et al. (2000)
	Classical Estrogen Receptors	– Reduced expression of NF-kB p65 and phosphorylated I-kBα – Attenuated the expression of active caspase-3 and reduction of apoptosis, and infiltration of leukocytes to the injury site.	Wei and Ma (2014)
	Mechanism mediated by ERα	– Inhibition of inflammatory gene transcription mediated by ER and NF-κB	Franco Rodriguez et al. (2013)
	ER-α36, a novel variant of ERα	– Enhanced neuroprotection by regulating ER-α36 expression	Zou et al. (2015)
	ER – Pathways	– Attenuation of manganese-induced ROS formation through phosphatidylinositol-3 kinase (PI3K)/Akt signaling pathway	Lee et al. (2009)
	ERα – ERβ – Pathways	– Increased TGF-α mRNA and protein levels and increased GLT - 1	Lee et al. (2012b)
	ER-Pathways	– Increased expression and release of TGF-β1 and TGF-β2 mediated by phosphotidylinositol 3-kinase (PI3K)/Akt	Dhandapani et al. (2005)
	ER-Pathways	– Decreased neuronal loss and apoptosis mediated by increasing neuronal p-ERK1/2 and Bcl-2 expression	Tsai et al. (2014)
	ER - Pathways	– Ameliorate TBI-induced depression-like behavior in rats by increasing neuronal p-ERK1/2 expression, associated with neuronal Bcl2 and BDNF expression	C.-C. Wang et al. (2016)
	ER - Pathways	– Attenuated the elevation of pERK1/2, an effect correlated with reduced infarct size. – Enhancement of MnSOD expression	Wakade et al. (2008)
	ERα	– Neuroprotection to hippocampal neurons by modulating the expression of Bcl-2 and Bax	Mosquera et al. (2014) and Sharma and Mehra (2008)
Raloxifene	ERβ mRNA levels	– Increased in amygdala.	Zhou et al. (2002)
	ER - Pathways	– Suppressed IL-1β-induced NF-κB activation (phosphorylation of p65) and translocation but did not affect phosphorylation of IκB	Li et al. (2014)
	ERα	– Neuroprotective action of raloxifene against hypoxia-induced damage in mouse hippocampal cells	Rzemieniec et al. (2015)
	ER - Pathways	– Reduced production of TNF-α and IL-1β 6 h after SCI	Ismailoglu et al. (2013)
Tamoxifen/Raloxifene	Potent transcriptional activators with ERβ at an AP1 site	– Element triggering the transcription of genes	Paech et al. (1997)
Tamoxifen and Raloxifene	Estrogen receptor-dependent pathway	– Suppressed microglial activation and neuronal cell death	Ishihara et al. (2015)
4OH-tamoxifen	Estrogen Receptor-Beta1	– Mediated gene transcription in neuronal cells	Pak et al. (2005)
Tamoxifen, Raloxifene, Ospemifene and Bazedoxifene	Mechanism involving Classical Estrogen Receptors	– Decreased the expression of IL-6 and IP-10 mRNA and protein levels	Cerciat et al. (2010)
Ospemifene and Bazedoxifene	Mechanism involving Classical Estrogen Receptors	– Anti-inflammatory actions by the inhibition of LPS-induced NF-κB p65 transactivation	Cerciat et al. (2010)

astrocytes through ER. Indeed, tamoxifen increases the expression of TGF-β1 as a result of augmented GLAST expression (Lee et al., 2009), besides promoting the release of TGF-β in cortical astrocyte, which depends on the membrane-associated ER that induces the phosphorylation of Akt (Dhandapani et al., 2005).

In spinal cord injury, tamoxifen showed antioxidant effect and recovery of locomotor activity mediated by the ERα (Mosquera et al., 2014; Sharma and Mehra, 2008). Furthermore, long-term administration of tamoxifen in ovariectomized rats reduced upregulation of BAX and downregulation of Bcl-2 proteins in the hippocampus by exerting its protective effect through ERα and in hippocampal neurons of male rats, after TBI, tamoxifen-induced anti-apoptotic proteins by the activation of the pERK1/2 signal pathway and Bcl-2 (Tsai et al., 2014). Similarly, tamoxifen demonstrated the reduction of neuronal death in TBI by the activation of ERK1/2 and Bcl-2. In this study, the researchers proposed that tamoxifen promoted cell survival by activating the RSK-ERK-Creb-Bcl-2 pathway. Also, tamoxifen increased some neurotrophic factors such as BDNF that are implicated in cell survival (C.-C. Wang et al., 2016). A study in cerebral ischemia showed that tamoxifen has beneficial effects by decreasing phospho-ERK1/2 and reducing the infarct size (Wakade et al., 2008). It also implies an antioxidant mechanism as it attenuated the production of the superoxide anion (Wakade et al., 2008). On the other hand, in brain trauma, the response of purinergic receptors (P2) results in the release of active ATP and ERK. In turn, ERK signaling is involved in the mechanisms of proliferation and differentiation in astrocytes after injury, as well as when calcium influx rules out the decreased ERK activation (Neary et al., 2003).

The ER-β and GPR30 expression levels under hypoxic conditions were not increased by raloxifene treatment in hippocampal neurons (Rzemieniec et al., 2015). On the contrary, in another study, the protective effect of raloxifene on hippocampal neurons was mediated by ERα, which triggers the increase of mitochondrial membrane potential, loss of the lactate dehydrogenase enzyme (LDH) and decreased neuronal survival. In astrocytes under oxygen glucose deprivation and hypoxic injuries, estrogens showed to change the expression of ERα and to induce neuroprotective effects (Al-Bader et al., 2011). This study suggested that these changes in ERα expression were mediated by the hypoxia-inducible factor-1 (HIF-1). For instance, HIF-1 has a pivotal role in the celladaptation to hypoxic conditions, is expressed in astrocytes under ischemic conditions, and is implicated in increasing glutathione, astrocytic survival, and the cell protection against glutamate toxicity (Badawi et al., 2012). Finally, tamoxifen and raloxifene also suppressmicroglial activation. Under LPS toxicity, the decrease of microglia activation induced by tamoxifen and raloxifeneinvolved the ER-mediated activation of gene promoters containing estrogen response element (ERE) and triggered a reduction of TNFα and IL-1β mRNA expression (Ishihara et al., 2015). Similarly, raloxifene decreased the concentration of IL-6 and TNF-α induced by spinal cord injury, which contributes to a reduction of iNOS (Ismailoglu et al., 2013).

7. Non-Genomic signaling mediated by SERMs: G/Protein coupled receptor for estrogens (GPR30)

Several studies have shown that the neuroprotective effect of tamoxifen persists even after the administration of ER blockers (Zhang

Table 6
Non-classic receptors: G protein coupled receptor for estrogen (GPR30) activation by SERMs.

SERM	Receptor	Main Findings	References
Raloxifene	Stereospecific neuroprotection	– Neuroprotective effect on dopamine transport	Callier et al. (2001)
		– Neuroprotective properties of Raloxifene in MPTP C57Bl/6 mice	
	G protein-coupled estrogen receptor	– Activation of striatal Akt signaling and increased Bcl-2 and BDNF levels	Bourque et al. (2014)
		– Activation of Nrf2 and antioxidant response element (ARE)	Abdelhamid et al. (2011)
		– Activation of ERK, EGFR, and CREB pathways	Karki et al. (2014b)
		– Enhanced expression of GLT1 and GLAST	
		– GPR30 trigged a rapid signaling of intracellular Ca^{2+}, activation of PI3K/Akt and Src/ERK/CREB pathways exhibiting anti-apoptotic mechanisms of neuroprotection	Abdelhamid et al. (2011)
17β-estradiol (E2)		– Increased astrocytic expression of GLT-1 and its molecular mechanism is involved by cAMP/PKA pathways, CREB, and NF-kB p50 and NF-kB p65	Lee et al. (2012a)
Tamoxifen		– Increased TGF-α mRNA and protein levels and increased GLT - 1	Lee et al. (2012b)
		– GPR30 activated several pathways as ERK 1/2, PI3K, cAMP and PKA and increased the expression of transforming growth factor (TGF) and GLT1 in astrocytes.	Lee et al. (2012b)

et al., 2007). Therefore, this suggests that tamoxifen might bind to others receptors such as GPR30. GPR30, also called as G-protein estrogens receptor-1 (GPER1), is a member of superfamily G-protein receptors implicated in rapid kinase signaling involved in neuroprotection and pro-survival mechanisms such as Akt, ERK and PI3K signaling (Arevalo et al., 2015; Tang et al., 2014) (Table 6). Indeed, GPR30 triggers a rapid response by decreasing the pro-apoptotic JNKs (Tang et al., 2014).

Raloxifene has displayed protective actions on dopaminergic neurons under MPTP toxicity in C57BL/6 male mice by a mechanism involving the activation of GPR30, AKT phosphorylation, and positive modulation of Bcl-2 and BDNF, but not of GDNF (Bourque et al., 2014). However, in another toxicity study using 6-OHDA, it was found that treatment with 17β-estradiol also increased GDNF protein levels both in the substantia nigra and striatum, inducing protection of nigrostriatal dopaminergic neurons in a male rat model of PD (Campos et al., 2012). GPR30 activation is associated with the promotion of the expression of GDNF in dopaminergic neuronsinduced by 17β-estradiol as a mechanism against MPTP toxicity (Bessa et al., 2015). Raloxifene also induced a stereospecific neuroprotection acting on dopamine transport (DAT) and dopamine depletion caused by MPTP toxicity in neurons of the substantia nigra and the striatum (Callier et al., 2001).

Tamoxifen increased the expression of glutamate transporter (GLT-1) in astrocytes, decreased manganese levels, and enhanced the uptake of glutamate, thus preventing excitotoxicity (Lee et al., 2012b). In this regard, tamoxifen acted via GPR30 by activating several signaling factors such as ERK 1/2, PI3K, cAMP, and PKA and by increasing the expression of the transforming growth factor (TGF) and GLT-1 in astrocytes (Lee et al., 2012b). Tamoxifen also improved the expression of TGF and GLT-1 by stimulating CREB and NF-κB (Karki et al., 2013). The epidermal growth factor (EGF) receptor (EGFR) plays an important role of expression of GLT-1 in astrocytes by stimulating the TGF-α/EGFR pathway. In this regard, GPR30 stimulates EGFR by transactivation (Lee et al., 2012b; Mo et al., 2013).

Raloxifene promotes the expression of GLT-1 and GLAST in astrocytes by the activation of ERK, EGFR, and CREB pathways and signaling by GPR30 (Karki et al., 2013, 2014c). In another model the oxygen-glucose deprivation in cortical neurons, raloxifene prevented apoptosis and cell death by a non-genomic path through its binding to GPR30, triggering rapid signaling of intracellular Ca^{2+}, activating the PI3K/Akt and Src/ERK/CREB pathways exhibiting anti-apoptotic mechanisms of neuroprotection (Abdelhamid et al., 2011). Additionally, raloxifene triggers the activation of the transcription factor Nrf2 and the antioxidant response element (ARE), which is anER-independent promoter of redox homeostasis in neurons under oxygen-glucose deprivation (Abdelhamid et al., 2011). The activation of ARE is implicated in the expression of genes that are protective against oxidative stress and is dependent on Nrf2 activity (Lee et al., 2003).

To date, several studies also support the neuroprotective effects of E2 associated to GPR30. For example, E2 increases the astrocytic expression of GLT-1, and its molecular mechanism incolves cAMP/PKA, CREB, and NF-κB p50 and NF-κB p65 pathways, which are activated by EGF/EGFR regulated through GPR30 (Lee et al., 2012a). In this regard, a positive modulation of NF-κB in the expression of GLAST-1 (rodent) and EAAT1 (human) through EGF has also been reported (Karki et al., 2015). On the contrary, it was found that the transcription factor Yin Yang 1 (YY1), which is a repressor of the EAAT1 promoter that are induced by manganese toxicity, can trigger the downregulation of EAAT1 and TGF-α expression (Karki et al., 2017, 2015). Another study reported the negative effects of YY1 on EAAT1 expression by TNF-α action (Karki et al., 2014b), thus triggering increased production of glutamate, which in turn is related to neurodegeneration. Although, it is known the role of EGF stimulating the expression of GLT-1 through GPR30, and the opposite effects of YY1, enhancing glutamate levels and neurodegeneration, it is not yet clear whether all SERMs affect NF-κB through GPR30 or can also affect YY1 activity (Karki et al., 2017, 2015) or stimulate protective factors like the EGF (Karki et al., 2015).

8. Tamoxifen-induced differentiation of progenitor cells

Recently, some studies have assessed the potential of neural progenitor cells and oligodendrocytes precursors cells (OPCs) as a strategy for regeneration against CNS diseases and injuries such as TBI (X. Wang et al., 2016) and MS (Gonzalez et al., 2016). NPCs have multipotent capacities to become neurons, astrocytes and oligodendrocytes (Suh et al., 2007). Estrogens have shown increased proliferation of neural progenitor cells and their response is mediated by ER-β and activation of ERK signaling, which is implicated in cell cycle regulation and cell proliferation (Wang et al., 2008). Neural stem/progenitor cells were reported to differentiate into oligodendrocytes by the actions of estrogens, but this action is not associated with ER activation (Okada et al., 2010). Although the proliferation is associated with activation of ER, it triggers the phosphorylation of MAPK/ERK (Okada et al., 2010).

Tamoxifen has effects on axonal and myelin preservation under spinal cord injury, which might favor locomotion recovery in cats (de la Torre Valdovinos et al., 2016). The beneficial effect of tamoxifen on myelin might be related to the differentiation of oligodendrocyte progenitor cells. This, in turn, may favor the remyelination *in vivo* by tamoxifen and is mediated by ER-α, ER-β and GPR30 (Gonzalez et al., 2016). In this same study, tamoxifen triggered differentiation response by binding to ERα and ERβ, which promotes ERK 1/2 and CREB activities (Gonzalez et al., 2016). Tamoxifen is also a potent inducer of oligodendrocyte progenitor cells differentiation by modulating GPR30 that increases the intracellular calcium levels thus activating the adenylyl cyclase (AC) and as a result stimulating PKC-α and CREB1 (Gonzalez et al., 2016). Using high throughput screening assays, raloxifene, toremifene and tamoxifen promoted the differentiation of oligodendrocyte progenitor cells through ER-β, which triggers the activation of PI3K/Akt/mTOR signaling pathway (Lariosa-Willingham et al., 2016).

Rapamycin targeted in mammalian cells or mTOR has an important role in oligodendrocyte progenitor cells differentiation. The mTOR phosphorylation *in vivo* is implicated in signaling of immature oligodendrocyte stage, and regulated the expression of genes related to myelin and suppressed the expression of transcriptional repressors during oligodendrocyte progenitor cells differentiation (Tyler et al., 2009). Moreover, mTOR is implicated in the process of neurogenesis due to the increase of proliferation and differentiation of neural stem cell (NSC) in the hippocampus of aged mice (Romine et al., 2015), and previous study indicated that TBI increases the NSC proliferation by mTORC1 activation in the hippocampus (X. Wang et al., 2016). Thus, available evidence suggests that tamoxifen is involved in the differentiation of oligodendrocyte progenitor cells (Gonzalez et al., 2016) and the proliferation of astrocytes of male wistar rats after injury (Franco Rodriguez et al., 2013). Therefore, tamoxifen and other SERMs have become therapeutic targets for inflammatory and demyelinating diseases not only as agents for direct treatment with potential protection against ROS, but also for their contribution in the differentiation of oligodendrocyte progenitor cells and oligodendrocytes that form myelin. However, more research is needed to investigate their molecular mechanism of action.

9. Tamoxifen-inducible Cre-loxP system for fate-mapping

Tamoxifen, 4-hydroxytamoxifen, and endoxifen induced astrogliogenesis after spinal cord injury in female Balb/c mice and promoted the differentiation of oligodendrocyte progenitor cells in a form independent of the ER activation (Barabási et al., 2016). Some previous studies have described the capacity of astrocytes to differentiate into stem cells under the conditions of injury using a tamoxifen-inducible Cre-loxP system (Buffo et al., 2008; Sirko et al., 2013). For instance, the Cre/lox system is a molecular technique that controls site-specific DNA recombination in different regions of brain. The action of Cre/lox system is mediated by tamoxifen, which binds to Cre/ER and releases HSP90 to be translocated into the nucleus and to mediate the specific recombination of a site (Slezak et al., 2007). Therefore, knowing the kinetics and metabolism of tamoxifen when using a CRE-loXp system, which is an experimental alternative for the genetics and cell biology of mammals, is important not only for the role of a particular gene in both development and pathogenesis, but also to define the dosage to avoid over-recombination (McLellan et al., 2017; Ray et al., 2000; Sauer, 1998).

9.1. Notch-1 receptor

Notch proteins are ligand-activated transmembrane receptors (Artavanis-Tsakonas et al., 1995; Blaumueller and Artavanis-Tsakonas, 1997). Notch has significant effects on the CNS. For example, Notch regulates both neurogenesis and cell cycle activity to coordinate the differentiation of precursor cell in the eyes of Drosophila (Bhattacharya et al., 2017). Also, Notch-1 is part of the signaling mechanisms involved in the proliferation of astrocytes under conditions of injury (Kato et al., 2018; Zhang et al., 2015), astrocytic functional maturation (Hasel et al., 2017) and the astrocytic expression of GLT-1 (Lee et al., 2017).

Notch 1 activity is required for reactive astrocyte proliferation in the peri-infarct area after stroke (Shimada et al., 2011). After tamoxifen treatment, GFAP-CreER™:Notch-1 conditional knockout mice had a significantly decreased number of proliferating and RC2-positive reactive astrocytes. Tamoxifen treatment also led to an increased number of CD45-positive cells that invaded the peri-infarct area. There is evidence that both the γ-secretase and the endothelin type B receptor (ETBR) are important in Notch-1 signaling. The γ-secretase in astrocytes is involved in the proliferation of reactive astroglia (Shimada et al., 2011). Also, previous studies have shown that γ-secretase increases its activity under the condition of ischemia (Arumugam et al., 2011; Pluta et al., 2013) and that treatment with the γ-secretase inhibitor L-685,458 after a stroke attenuated cerebral ischemia-induced caspase-3 cleavage and apoptotic cell death (Polavarapu et al., 2008) and modulation of neuroinflammation and neurodegenerative diseases (Gandy and Wustman, 2011; Wolfe, 2008).

Another molecule that has been found to mediate astrogliosis through Notch-1 is the Type B endothelin receptor (ETBR). Astrocytes proliferation through Notch-1 is related to increased expression of STAT3 and Jagged1, and induction of ETBR in male C57BL/6J mice (LeComte et al., 2015). Astrocytes do express an endothelin receptor. In normal conditions, endothelin-1 (ET-1) is not detectable in astrocytes, but in pathological conditions it is highly expressed and triggers hypertrophy and reactive gliosis (Hostenbach et al., 2016). Endothelin-1 induced reactive gliosis via activation of c-Jun/JNK pathway (Gadea et al., 2008). Using a Cre/ER system for tamoxifen-induced ETBR in the case of multiple sclerosis, it was possible to confirm that the astrocyte-derived endothelin-1 inhibits remyelination through Notch activation (Hammond et al., 2014, 2015; Reddel et al., 1983). However, several trials are still required to fully understand the role of Notch-1 and its signaling in different pathologies, and also to understand when its role or activation is harmful or beneficial for brain tissues and whether the use of SERMs may contribute to the activation of survival pathways or neuroprotection through this receptor.

9.2. Inositol 1, 4, 5-trisphosphate receptor type 2 (ITPR2)

Inositol 1, 4, 5-trisphosphate receptor type 2 (ITPR2), also called IP3R2, is a receptor for inositol triphosphate (IP3), a second messenger that triggers intracellular calcium release by IP3-sensitive channels. Ca^{2+} signaling modulates synaptic transmission (Hirase et al., 2004) and intracellular increase of Ca^{2+} releases gliotransmitters such as glutamate, ATP, and D-serine (Martineau, 2013). Glutamate and D-serine increases synaptic plasticity through NMDAR (Padmashri et al., 2015; Shigetomi et al., 2013b), and ATP supports neuronal transmission and survival.

About the mechanisms involved in the release of gliotransmitters, it was found studying a mutant IP3R2 mice, generated using the tamoxifen-induced Cre-recombinase technique that the activation of IP3R2 in astrocytes was due to increased Ca^{2+} levels which was related to motor skill learning, while the expression of a mutant IP3R2 plus fluorocitrate (FC) treatment had a negative impact on learning (Padmashri et al., 2015). Nonetheless, in response to brain injury, Ca^{2+} signaling is required for astrogliosis, and the activation of IP3R2 induced by Ca^{2+} and IP3 releases ATP, ET1, and glutamate from the injury site (Kanemaru et al., 2013). In ischemic stroke, astrocytic deletion of IP3R2 reduced neural damage, cell death, PLC/IP3R2 Ca^{2+} signaling, glutamate excitotoxicity from astrocytes, and attenuated reactive-like astroglial morphology in the adult male and female IP3R2KO (Li et al., 2015).

9.3. Cannabinoid receptors (CBR)

CBRs are expressed in hippocampal astrocytes and are part of the G protein-coupled seven-transmembrane receptor (GPCR) superfamily (Navarrete and Araque, 2008). Tamoxifen and its metabolites exhibit affinity towards cannabinoids subtype 1 and 2 receptors (CB1R and CB2Rs) (Ford et al., 2016). The Z-hydroxytamoxifen showed higher affinity for CB1R and CB2R than Z-Tamoxifen or Z-Endoxifen, but 4-hydroxytamoxifen showed high affinity for CB2R (Ford et al., 2016). Activation of the cannabinoid system promotes the communication between astrocytes and neurons, triggering astrocyte Ca^{2+} signaling, the release of glutamate, and the activation of the neuronal NMDAR. Through Cre/loxP system in GFAP-CB1-KO mice, treatment with tamoxifen showed that deletion of CB1 receptors in astrocytes produced a detriment in ObR and response to leptin in astrocytes (Bosier et al., 2013). Leptin is required for the maintenance of brain energy stores such as glycogen and synaptic transmission (Bosier et al., 2013; Kim et al., 2014). On the other hand, a study using a conditional mutant male mice lacking the type-1 cannabinoid receptors CB1R suggested that the consumption of marijuana alters hippocampal-dependent spatial working memory *by* activating the CB1R in astrocytes but no in the CB(1)R in glutamatergic or GABAergic neurons (Han et al., 2012). Astrocytes seem to potentiate synaptic transmission through CB1R, which stimulatesthe release of glutamate from astrocytes (Navarrete and Araque, 2008). In addition, the endocannabinoid system supports neuron-astrocyte communication through CB1R-mediated phospholipase C-dependent Ca^{2+} mobilization from internal stores and triggers the release of glutamate that activates neuronal NMDAR (Navarrete and Araque, 2008).

10. Concluding remarks

In conclusion, the evidence presented here indicates that SERMs such as tamoxifen and raloxifene, in addition to their action in other organs, have a fundamental role at the CNS level. These include antioxidant, antiapoptotic properties, reduction of microglia activation by mechanisms independent of estrogen receptors and trigger numerous mechanisms of survival and differentiation in neurons, astrocytes, microglia and oligodendroglia. Should these benefits be added to the lack of treatment that currently have several brain pathologies, SERMs become an promising therapeutic alternative to decrease brain damage or slow down the progress of these diseases. However, it is evident that SERMs not only have benefits for the treatment or reduction of secondary events in brain pathologies, but are also involved in the differentiation of cells such as oligodendrocyte precursors. Until nowadays, it has not been investigated whether SERMs have clear effects on neuronal stem cells and the pharmacokinetics of tamoxifen at the brain level have not been well characterized yet. Therefore, future studies on this aspect and the clinical advance of the use of SERMs in the CNS are presented with a good projection at the therapeutic level.

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Conflict of interest

The authors declare no conflict of interest.

References

Abdelhamid, R., Luo, J., Vandevrede, L., Kundu, I., Michalsen, B., Litosh, V.A., et al., 2011. Benzothiophene selective estrogen receptor modulators provide neuroprotection by a novel GPR30-dependent mechanism. ACS Chem. Neurosci. 2 (5), 256–268. https://doi.org/10.1021/cn100106a.

Acaz-Fonseca, E., Sanchez-Gonzalez, R., Azcoitia, I., Arevalo, M.A., Garcia-Segura, L.M., 2014. Role of astrocytes in the neuroprotective actions of 17beta-estradiol and selective estrogen receptor modulators. Mol. Cell. Endocrinol. 389 (1–2), 48–57. https://doi.org/10.1016/j.mce.2014.01.009.

Ahmad, A., Shahabuddin, S., Sheikh, S., Kale, P., Krishnappa, M., Rane, R.C., Ahmad, I., 2010. Endoxifen, a new cornerstone of breast cancer therapy: demonstration of safety, tolerability, and systemic bioavailability in healthy human subjects. Clin. Pharmacol. Ther. 88 (6), 814–817. https://doi.org/10.1038/clpt.2010.196.

Al-Bader, M.D., Malatiali, S.A., Redzic, Z.B., 2011. Expression of estrogen receptor alpha and beta in rat astrocytes in primary culture: effects of hypoxia and glucose deprivation. Physiol. Res. 60 (6), 951–960.

Allaman, I., Gavillet, M., Belanger, M., Laroche, T., Viertl, D., Lashuel, H.A., Magistretti, P.J., 2010. Amyloid-beta aggregates cause alterations of astrocytic metabolic phenotype: impact on neuronal viability. J. Neurosci. 30 (9), 3326–3338. https://doi.org/10.1523/JNEUROSCI.5098-09.2010.

Arevalo, M.A., Azcoitia, I., Garcia-Segura, L.M., 2015. The neuroprotective actions of oestradiol and oestrogen receptors. Nat. Rev. Neurosci. 16 (1), 17–29. https://doi.org/10.1038/nrn3856.

Arevalo, M.A., Diz-Chaves, Y., Santos-Galindo, M., Bellini, M.J., Garcia-Segura, L.M., 2012. Selective oestrogen receptor modulators decrease the inflammatory response of glial cells. J. Neuroendocrinol. 24 (1), 183–190. https://doi.org/10.1111/j.1365-2826.2011.02156.x.

Arevalo, M.A., Santos-Galindo, M., Bellini, M.J., Azcoitia, I., Garcia-Segura, L.M., 2010. Actions of estrogens on glial cells: implications for neuroprotection. Biochim. Biophys. Acta 1800 (10), 1106–1112. https://doi.org/10.1016/j.bbagen.2009.10.002.

Artavanis-Tsakonas, S., Matsuno, K., Fortini, M.E., 1995. Notch signaling. Science 268 (5208), 225–232.

Arumugam, T.V., Cheng, Y.L., Choi, Y., Choi, Y.H., Yang, S., Yun, Y.K., et al., 2011. Evidence that gamma-secretase-mediated Notch signaling induces neuronal cell death via the nuclear factor-kappaB-Bcl-2-interacting mediator of cell death pathway in ischemic stroke. Mol. Pharmacol. 80 (1), 23–31. https://doi.org/10.1124/mol.111.071076.

Ascenzi, P., Bocedi, A., Marino, M., 2006. Structure-function relationship of estrogen receptor alpha and beta: impact on human health. Mol. Aspects Med. 27 (4), 299–402. https://doi.org/10.1016/j.mam.2006.07.001.

Avila-Rodriguez, M., Garcia-Segura, L.M., Hidalgo-Lanussa, O., Baez, E., Gonzalez, J., Barreto, G.E., 2016. Tibolone protects astrocytic cells from glucose deprivation through a mechanism involving estrogen receptor beta and the upregulation of neuroglobin expression. Mol. Cell. Endocrinol. 433, 35–46. https://doi.org/10.1016/j.mce.2016.05.024.

Avila Rodriguez, M., Garcia-Segura, L.M., Cabezas, R., Torrente, D., Capani, F., Gonzalez, J., Barreto, G.E., 2014. Tibolone protects T98G cells from glucose deprivation. J. Steroid Biochem. Mol. Biol. 144 Pt B, 294–303. https://doi.org/10.1016/j.jsbmb.2014.07.009.

Badawi, Y., Ramamoorthy, P., Shi, H., 2012. Hypoxia-inducible factor 1 protects hypoxic astrocytes against glutamate toxicity. ASN Neuro 4 (4), 231–241. https://doi.org/10.1042/AN20120006.

Bagheri, M., Rezakhani, A., Nystrom, S., Turkina, M.V., Roghani, M., Hammarstrom, P., Mohseni, S., 2013. Amyloid beta(1–40)-induced astrogliosis and the effect of genistein treatment in rat: a three-dimensional confocal morphometric and proteomic study. PLoS One 8 (10), e76526. https://doi.org/10.1371/journal.pone.0076526.

Bagheri, M., Roghani, M., Joghataei, M.T., Mohseni, S., 2012. Genistein inhibits aggregation of exogenous amyloid-beta(1)(-)(4)(0) and alleviates astrogliosis in the hippocampus of rats. Brain Res. 1429, 145–154. https://doi.org/10.1016/j.brainres.2011.10.020.

Bajpai, P., Sangar, M.C., Singh, S., Tang, W., Bansal, S., Chowdhury, G., et al., 2013. Metabolism of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine by mitochondrion-targeted cytochrome P450 2D6: implications in Parkinson disease. J. Biol. Chem. 288 (6), 4436–4451. https://doi.org/10.1074/jbc.M112.402123.

Barabási, B., Csondor, A., Martín-Pozas, T., Sánchez, A.P., Antalffy, G., Siklós, L., et al., 2016. Effect of axotomy and 17β-estradiol on P2X7 receptor expression pattern in the hypoglossal nucleus of ovariectomized mice. Neuroscience 319, 107–115.

Barcia, C., Ros, C.M., Annese, V., Gomez, A., Ros-Bernal, F., Aguado-Yera, D., et al., 2011. IFN-gamma signaling, with the synergistic contribution of TNF-alpha, mediates cell specific microglial and astroglial activation in experimental models of Parkinson's disease. Cell Death Dis. 2, e142. https://doi.org/10.1038/cddis.2011.17.

Barreto, G., Santos-Galindo, M., Diz-Chaves, Y., Pernia, O., Carrero, P., Azcoitia, I., Garcia-Segura, L.M., 2009. Selective estrogen receptor modulators decrease reactive astrogliosis in the injured brain: effects of aging and prolonged depletion of ovarian hormones. Endocrinology 150 (11), 5010–5015. https://doi.org/10.1210/en.2009-0352.

Barreto, G., Veiga, S., Azcoitia, I., Garcia-Segura, L.M., Garcia-Ovejero, D., 2007. Testosterone decreases reactive astroglia and reactive microglia after brain injury in male rats: role of its metabolites, oestradiol and dihydrotestosterone. Eur. J. Neurosci. 25 (10), 3039–3046.

Barreto, G.E., Santos-Galindo, M., Garcia-Segura, L.M., 2014. Selective estrogen receptor modulators regulate reactive microglia after penetrating brain injury. Front. Aging Neurosci. 6, 132. https://doi.org/10.3389/fnagi.2014.00132.

Beach, T.G., Walker, R., McGeer, E.G., 1989. Patterns of gliosis in Alzheimer's disease and aging cerebrum. Glia 2 (6), 420–436. https://doi.org/10.1002/glia.440020605.

Bebo Jr., B.F., Dehghani, B., Foster, S., Kurniawan, A., Lopez, F.J., Sherman, L.S., 2009. Treatment with selective estrogen receptor modulators regulates myelin specific T-cells and suppresses experimental autoimmune encephalomyelitis. Glia 57 (7), 777–790. https://doi.org/10.1002/glia.20805.

Bessa, A., Campos, F.L., Videira, R.A., Mendes-Oliveira, J., Bessa-Neto, D., Baltazar, G., 2015. GPER: a new tool to protect dopaminergic neurons? Biochim. Biophys. Acta 1852 (10 Pt A), 2035–2041. https://doi.org/10.1016/j.bbadis.2015.07.004.

Bhat, H.K., Epelboym, I., 2004. Suppression of calbindin D28K in estrogen-induced hamster renal tumors. J. Steroid Biochem. Mol. Biol. 92 (5), 391–398. https://doi.org/10.1016/j.jsbmb.2004.07.009.

Bhattacharya, A., Li, K., Quiquand, M., Rimesso, G., Baker, N.E., 2017. The Notch pathway regulates the Second Mitotic Wave cell cycle independently of bHLH proteins. Dev. Biol. 431 (2), 309–320. https://doi.org/10.1016/j.ydbio.2017.08.035.

Bianchi, R., Verzini, M., Garbuglia, M., Giambanco, I., Donato, R., 1994. Mechanism of S100 protein-dependent inhibition of glial fibrillary acidic protein (GFAP) polymerization. Biochim. Biophys. Acta (BBA)-Mol. Cell Res. 1223 (3), 354–360.

Bindocci, E., Savtchouk, I., Liaudet, N., Becker, D., Carriero, G., Volterra, A., 2017. Three-dimensional Ca2+ imaging advances understanding of astrocyte biology. Science 356 (6339). https://doi.org/10.1126/science.aai8185.

Blasko, E., Haskell, C.A., Leung, S., Gualtieri, G., Halks-Miller, M., Mahmoudi, M., et al., 2009. Beneficial role of the GPR30 agonist G-1 in an animal model of multiple sclerosis. J. Neuroimmunol. 214 (1–2), 67–77. https://doi.org/10.1016/j.jneuroim.2009.06.023.

Blaumueller, C.M., Artavanis-Tsakonas, S., 1997. Comparative aspects of Notch signaling in lower and higher eukaryotes. Perspect. Dev. Neurobiol. 4 (4), 325–343.

Bondesson, M., Hao, R., Lin, C.Y., Williams, C., Gustafsson, J.A., 2015. Estrogen receptor signaling during vertebrate development. Biochim. Biophys. Acta 1849 (2), 142–151. https://doi.org/10.1016/j.bbagrm.2014.06.005.

Boocock, D.J., Maggs, J.L., White, I.N., Park, B.K., 1999. α-Hydroxytamoxifen, a genotoxic metabolite of tamoxifen in the rat: identification and quantification in vivo and in vitro. Carcinogenesis 20 (1), 153–160.

Bosier, B., Bellocchio, L., Metna-Laurent, M., Soria-Gomez, E., Matias, I., Hebert-Chatelain, E., et al., 2013. Astroglial CB1 cannabinoid receptors regulate leptin signaling in mouse brain astrocytes. Mol. Metab. 2 (4), 393–404. https://doi.org/10.1016/j.molmet.2013.08.001.

Boulos, A.S., Deshaies, E.M., Dalfino, J.C., Feustel, P.J., Popp, A.J., Drazin, D., 2011. Tamoxifen as an effective neuroprotectant in an endovascular canine model of stroke. J. Neurosurg. 114 (4), 1117–1126. https://doi.org/10.3171/2010.8.JNS09352.

Bourque, M., Morissette, M., Di Paolo, T., 2014. Raloxifene activates G protein-coupled estrogen receptor 1/Akt signaling to protect dopamine neurons in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mice. Neurobiol. Aging 35 (10), 2347–2356. https://doi.org/10.1016/j.neurobiolaging.2014.03.017.

Brawek, B., Garaschuk, O., 2017. Monitoring in vivo function of cortical microglia. Cell Calcium 64, 109–117. https://doi.org/10.1016/j.ceca.2017.02.011.

Brown, L.M., Gent, L., Davis, K., Clegg, D.J., 2010. Metabolic impact of sex hormones on obesity. Brain Res. 1350, 77–85. https://doi.org/10.1016/j.brainres.2010.04.056.

Bruce, A.J., Boling, W., Kindy, M.S., Peschon, J., Kraemer, P.J., Carpenter, M.K., et al., 1996. Altered neuronal and microglial responses to excitotoxic and ischemic brain injury in mice lacking TNF receptors. Nat. Med. 2 (7), 788–794.

Bruck, D., Wenning, G.K., Stefanova, N., Fellner, L., 2016. Glia and alpha-synuclein in neurodegeneration: a complex interaction. Neurobiol. Dis. 85, 262–274. https://doi.org/10.1016/j.nbd.2015.03.003.

Buffo, A., Rite, I., Tripathi, P., Lepier, A., Colak, D., Horn, A.P., et al., 2008. Origin and progeny of reactive gliosis: a source of multipotent cells in the injured brain. Proc. Natl. Acad. Sci. USA 105 (9), 3581–3586. https://doi.org/10.1073/pnas.0709002105.

Buffo, A., Rolando, C., Ceruti, S., 2010. Astrocytes in the damaged brain: molecular and cellular insights into their reactive response and healing potential. Biochem. Pharmacol. 79 (2), 77–89. https://doi.org/10.1016/j.bcp.2009.09.014.

Burda, J.E., Bernstein, A.M., Sofroniew, M.V., 2016. Astrocyte roles in traumatic brain injury. Exp. Neurol. 275 (Pt 3), 305–315. https://doi.org/10.1016/j.expneurol.2015.03.020.

Cabezas, R., Avila, M., Gonzalez, J., El-Bacha, R.S., Baez, E., Garcia-Segura, L.M., et al., 2014. Astrocytic modulation of blood brain barrier: perspectives on Parkinson's disease. Front. Cell Neurosci. 8, 211. https://doi.org/10.3389/fncel.2014.00211.

Callier, S., Morissette, M., Grandbois, M., Pelaprat, D., Di Paolo, T., 2001. Neuroprotective properties of 17beta-estradiol, progesterone, and raloxifene in MPTP C57Bl/6 mice. Synapse 41 (2), 131–138. https://doi.org/10.1002/syn.1067.

Campos, F.L., Cristovao, A.C., Rocha, S.M., Fonseca, C.P., Baltazar, G., 2012. GDNF contributes to oestrogen-mediated protection of midbrain dopaminergic neurones. J. Neuroendocrinol. 24 (11), 1386–1397. https://doi.org/10.1111/j.1365-2826.2012.02348.x.

Capozzi, M.E., McCollum, G.W., Penn, J.S., 2014. The role of cytochrome P450 epoxygenases in retinal angiogenesis. Invest. Ophthalmol. Vis. Sci. 55 (7), 4253–4260. https://doi.org/10.1167/iovs.14-14216.

Carniglia, L., Durand, D., Caruso, C., Lasaga, M., 2013. Effect of NDP-alpha-MSH on PPAR-gamma and -beta expression and anti-inflammatory cytokine release in rat astrocytes and microglia. PLoS One 8 (2), e57313. https://doi.org/10.1371/journal.pone.0057313.

Cerbai, F., Lana, D., Nosi, D., Petkova-Kirova, P., Zecchi, S., Brothers, H.M., et al., 2012. The neuron-astrocyte-microglia triad in normal brain ageing and in a model of neuroinflammation in the rat hippocampus. PLoS One 7 (9), e45250. https://doi.org/10.1371/journal.pone.0045250.

Cerciat, M., Unkila, M., Garcia-Segura, L.M., Arevalo, M.A., 2010. Selective estrogen receptor modulators decrease the production of interleukin-6 and interferon-gamma-inducible protein-10 by astrocytes exposed to inflammatory challenge in vitro. Glia 58 (1), 93–102. https://doi.org/10.1002/glia.20904.

Céspedes, Á.E., Arango, C.A., Cardona, G.P., 2013. Análisis comparativo de marcadores de lesión en modelos de isquemia cerebral focal y global en ratas. Biomédica 33 (2), 292–305.

Cipolla, M.J., Godfrey, J.A., Wiegman, M.J., 2009. The effect of ovariectomy and estrogen on penetrating brain arterioles and blood-brain barrier permeability. Microcirculation 16 (8), 685–693. https://doi.org/10.3109/10739680903164131.

Colangelo, A.M., Alberghina, L., Papa, M., 2014. Astrogliosis as a therapeutic target for neurodegenerative diseases. Neurosci. Lett. 565, 59–64. https://doi.org/10.1016/j.neulet.2014.01.014.

Colon, J.M., Torrado, A.I., Cajigas, A., Santiago, J.M., Salgado, I.K., Arroyo, Y., Miranda, J.D., 2016. Tamoxifen administration immediately or 24 hours after spinal cord injury improves locomotor recovery and reduces secondary damage in female rats. J. Neurotrauma 33 (18), 1696–1708. https://doi.org/10.1089/neu.2015.4111.

Cui, J., Shen, Y., Li, R., 2013. Estrogen synthesis and signaling pathways during aging: from periphery to brain. Trends Mol. Med. 19 (3), 197–209. https://doi.org/10.1016/j.molmed.2012.12.007.

Czarnecka, A.M., Niedzwiedzka, M., Porta, C., Szczylik, C., 2016. Hormone signaling pathways as treatment targets in renal cell cancer (Review). Int. J. Oncol. 48 (6), 2221–2235. https://doi.org/10.3892/ijo.2016.3460.

Chakraborti, A., Allen, A., Allen, B., Rosi, S., Fike, J.R., 2012. Cranial irradiation alters dendritic spine density and morphology in the hippocampus. PLoS One 7 (7), e40844. https://doi.org/10.1371/journal.pone.0040844.

Chalvon-Demersay, T., Blachier, F., Tome, D., Blais, A., 2017. Animal models for the study of the relationships between diet and obesity: a focus on dietary protein and estrogen deficiency. Front. Nutr. 4, 5. https://doi.org/10.3389/fnut.2017.00005.

Chan, A., Magnus, T., Gold, R., 2001. Phagocytosis of apoptotic inflammatory cells by microglia and modulation by different cytokines: mechanism for removal of apoptotic cells in the inflamed nervous system. Glia 33 (1), 87–95.

Chang, B.Y., Kim, S.A., Malla, B., Kim, S.Y., 2011. The Effect of Selective Estrogen Receptor Modulators (SERMs) on the tamoxifen resistant breast cancer cells. Toxicol. Res. 27 (2), 85–93. https://doi.org/10.5487/TR.2011.27.2.085.

Chodobski, A., Zink, B.J., Szmydynger-Chodobska, J., 2011. Blood-brain barrier pathophysiology in traumatic brain injury. Transl. Stroke Res. 2 (4), 492–516. https://doi.org/10.1007/s12975-011-0125-x.

Dauchy, S., Dutheil, F., Weaver, R.J., Chassoux, F., Daumas-Duport, C., Couraud, P.O., et al., 2008. ABC transporters, cytochromes P450 and their main transcription factors: expression at the human blood-brain barrier. J. Neurochem. 107 (6), 1518–1528. https://doi.org/10.1111/j.1471-4159.2008.05720.x.

de la Torre Valdovinos, B., Duenas Jimenez, J.M., Estrada, I.J., Banuelos Pineda, J., Franco Rodriguez, N.E., Lopez Ruiz, J.R., et al., 2016. Tamoxifen promotes axonal preservation and gait locomotion recovery after spinal cord injury in cats. J. Vet. Med. 2016, 9561968. https://doi.org/10.1155/2016/9561968.

Dehal, S.S., Kupfer, D., 1999. Cytochrome P-450 3A and 2D6 catalyze ortho hydroxylation of 4-hydroxytamoxifen and 3-hydroxytamoxifen (droloxifene) yielding tamoxifen catechol: involvement of catechols in covalent binding to hepatic proteins. Drug Metab. Dispos. 27 (6), 681–688.

Derugin, N., Wendland, M., Muramatsu, K., Roberts, T.P., Gregory, G., Ferriero, D.M., Vexler, Z.S., 2000. Evolution of brain injury after transient middle cerebral artery occlusion in neonatal rats. Stroke 31 (7), 1752–1761.

Desta, Z., Ward, B.A., Soukhova, N.V., Flockhart, D.A., 2004. Comprehensive evaluation of tamoxifen sequential biotransformation by the human cytochrome P450 system in vitro: prominent roles for CYP3A and CYP2D6. J. Pharmacol. Exp. Ther. 310 (3), 1062–1075. https://doi.org/10.1124/jpet.104.065607.

Dhandapani, K.M., Brann, D.W., 2003. Neuroprotective effects of estrogen and tamoxifen in vitro. Endocrine 21 (1), 59–66.

Dhandapani, K.M., Wade, F.M., Mahesh, V.B., Brann, D.W., 2005. Astrocyte-derived transforming growth factor-{beta} mediates the neuroprotective effects of 17{beta}-estradiol: involvement of nonclassical genomic signaling pathways. Endocrinology 146 (6), 2749–2759. https://doi.org/10.1210/en.2005-0014.

Di, X., Goforth, P.B., Bullock, R., Ellis, E., Satin, L., 2000. Mechanical injury alters volume activated ion channels in cortical astrocytes. Acta Neurochir. Suppl. 76, 379–383.

Dickson, D.W., 2012. Parkinson's disease and parkinsonism: neuropathology. Cold Spring Harb. Perspect. Med. 2 (8). https://doi.org/10.1101/cshperspect.a009258.

Ditkoff, E.C., Crary, W.G., Cristo, M., Lobo, R.A., 1991. Estrogen improves psychological function in asymptomatic postmenopausal women. Obstet. Gynecol. 78 (6), 991–995.

Dittmar, A.J., Drozda, A.A., Blader, I.J., 2016. Drug repurposing screening identifies novel compounds that effectively inhibit toxoplasma gondii growth. mSphere 1 (2). https://doi.org/10.1128/mSphere.00042-15.

Dluzen, D.E., McDermott, J.L., Anderson, L.I., 2001. Tamoxifen eliminates estrogen's neuroprotective effect upon MPTP-induced neurotoxicity of the nigrostriatal dopaminergic system. Neurotox. Res. 3 (3), 291–300.

Dluzen, D.F., Sun, D., Salzberg, A.C., Jones, N., Bushey, R.T., Robertson, G.P., Lazarus, P., 2014. Regulation of UDP-glucuronosyltransferase 1A1 expression and activity by microRNA 491–3p. J. Pharmacol. Exp. Ther. 348 (3), 465–477. https://doi.org/10.1124/jpet.113.210658.

DonCarlos, L.L., Azcoitia, I., Garcia-Segura, L.M., 2009. Neuroprotective actions of selective estrogen receptor modulators. Psychoneuroendocrinology 34 (Suppl. 1), S113–S122. https://doi.org/10.1016/j.psyneuen.2009.04.012.

Dringen, R., Scheiber, I.F., Mercer, J.F., 2013. Copper metabolism of astrocytes. Front. Aging Neurosci. 5, 9. https://doi.org/10.3389/fnagi.2013.00009.

Eberling, J.L., Wu, C., Tong-Turnbeaugh, R., Jagust, W.J., 2004. Estrogen-and tamoxifen-associated effects on brain structure and function. Neuroimage 21 (1), 364–371.

Elloso, M.M., Phiel, K., Henderson, R.A., Harris, H.A., Adelman, S.J., 2005. Suppression of experimental autoimmune encephalomyelitis using estrogen receptor-selective ligands. J. Endocrinol. 185 (2), 243–252. https://doi.org/10.1677/joe.1.06063.

Ernst, T., Chang, L., Cooray, D., Salvador, C., Jovicich, J., Walot, I., et al., 2002. The effects of tamoxifen and estrogen on brain metabolism in elderly women. J. Natl. Cancer Inst. 94 (8), 592–597.

Fabian, C., Tilzer, L., Sternson, L., 1981. Comparative binding affinities of tamoxifen, 4-hydroxytamoxifen, and desmethyltamoxifen for estrogen receptors isolated from human breast carcinoma: correlation with blood levels in patients with metastatic breast cancer. Biopharm. Drug Dispos. 2 (4), 381–390.

Fam, B.C., Morris, M.J., Hansen, M.J., Kebede, M., Andrikopoulos, S., Proietto, J., Thorburn, A.W., 2007. Modulation of central leptin sensitivity and energy balance in a rat model of diet-induced obesity. Diabetes Obes. Metab. 9 (6), 840–852. https://doi.org/10.1111/j.1463-1326.2006.00653.x.

Fam, S.R., Gallagher, C.J., Salter, M.W., 2000. P2Y(1) purinoceptor-mediated Ca(2+) signaling and Ca(2+) wave propagation in dorsal spinal cord astrocytes. J. Neurosci. 20 (8), 2800–2808.

Farfan-Garcia, E.D., Castillo-Hernandez, M.C., Pinto-Almazan, R., Rivas-Arancibia, S., Gallardo, J.M., Guerra-Araiza, C., 2014. Tibolone prevents oxidation and ameliorates cholinergic deficit induced by ozone exposure in the male rat hippocampus. Neurochem. Res. 39 (9), 1776–1786. https://doi.org/10.1007/s11064-014-1385-0.

Farina, C., Aloisi, F., Meinl, E., 2007. Astrocytes are active players in cerebral innate immunity. Trends Immunol. 28 (3), 138–145. https://doi.org/10.1016/j.it.2007.01.005.

Feigin, V.L., Barker-Collo, S., Krishnamurthi, R., Theadom, A., Starkey, N., 2010. Epidemiology of ischaemic stroke and traumatic brain injury. Best Pract. Res. Clin. Anaesthesiol. 24 (4), 485–494. https://doi.org/10.1016/j.bpa.2010.10.006.

Feng, Y., Fratkins, J.D., LeBlanc, M.H., 2004. Treatment with tamoxifen reduces hypoxic-ischemic brain injury in neonatal rats. Eur. J. Pharmacol. 484 (1), 65–74.

Fernandez-Fernandez, S., Almeida, A., Bolanos, J.P., 2012. Antioxidant and bioenergetic coupling between neurons and astrocytes. Biochem. J. 443 (1), 3–11. https://doi.org/10.1042/BJ20111943.

Feustel, P.J., Jin, Y., Kimelberg, H.K., 2004. Volume-regulated anion channels are the predominant contributors to release of excitatory amino acids in the ischemic cortical penumbra. Stroke 35 (5), 1164–1168. https://doi.org/10.1161/01.STR.0000124127.57946.a1.

Fletcher, J.M., Lalor, S.J., Sweeney, C.M., Tubridy, N., Mills, K.H., 2010. T cells in multiple sclerosis and experimental autoimmune encephalomyelitis. Clin. Exp. Immunol. 162 (1), 1–11. https://doi.org/10.1111/j.1365-2249.2010.04143.x.

Ford, B.M., Franks, L.N., Radominska-Pandya, A., Prather, P.L., 2016. Tamoxifen isomers and metabolites exhibit distinct affinity and activity at cannabinoid receptors: potential scaffold for drug development. PLoS One 11 (12), e0167240. https://doi.org/10.1371/journal.pone.0167240.

Franco Rodriguez, N.E., Duenas Jimenez, J.M., De la Torre Valdovinos, B., Lopez Ruiz, J.R., Hernandez Hernandez, L., Duenas Jimenez, S.H., 2013. Tamoxifen favoured the rat sensorial cortex regeneration after a penetrating brain injury. Brain Res. Bull. 98, 64–75. https://doi.org/10.1016/j.brainresbull.2013.07.007.

Fuente-Martin, E., Garcia-Caceres, C., Morselli, E., Clegg, D.J., Chowen, J.A., Finan, B., et al., 2013. Estrogen, astrocytes and the neuroendocrine control of metabolism. Rev. Endocr. Metab. Disord. 14 (4), 331–338. https://doi.org/10.1007/s11154-013-9263-7.

Gabai, V.L., Yaglom, J.A., Volloch, V., Meriin, A.B., Force, T., Koutroumanis, M., et al., 2000. Hsp72-mediated suppression of c-Jun N-terminal kinase is implicated in development of tolerance to caspase-independent cell death. Mol. Cell. Biol. 20 (18), 6826–6836.

Gadea, A., Schinelli, S., Gallo, V., 2008. Endothelin-1 regulates astrocyte proliferation and reactive gliosis via a JNK/c-Jun signaling pathway. J. Neurosci. 28 (10), 2394–2408. https://doi.org/10.1523/JNEUROSCI.5652-07.2008.

Galván-Ramírez, M., Gutiérrez-Maldonado, A., Dueñas-Jiménez, J., Rodríguez-Pérez, L., Troyo-Sanromán, R., 2016. Effect of 17β-estradiol and progesterone on astrocytes infected with Toxoplasma. J. Adv. Parasitol 3 (1), 22–31.

Gallagher, C.J., Salter, M.W., 2003. Differential properties of astrocyte calcium waves mediated by P2Y1 and P2Y2 receptors. J. Neurosci. 23 (17), 6728–6739.

Gambacciani, M., Levancini, M., 2014. Hormone replacement therapy and the prevention of postmenopausal osteoporosis. Prz Menopauzalny 13 (4), 213–220. https://doi.org/10.5114/pm.2014.44996.

Gambaro, S.E., Robert, M.C., Tiribelli, C., Gazzin, S., 2016. Role of brain cytochrome P450 mono-oxygenases in bilirubin oxidation-specific induction and activity. Arch. Toxicol. 90 (2), 279–290. https://doi.org/10.1007/s00204-014-1394-4.

Gandy, S., Wustman, B., 2011. New pathway links gamma-secretase to inflammation and memory while sparing notch. Ann. Neurol. 69 (1), 5–7. https://doi.org/10.1002/ana.22310.

Gatson, J.W., Liu, M.M., Abdelfattah, K., Wigginton, J.G., Smith, S., Wolf, S., et al., 2012. Estrone is neuroprotective in rats after traumatic brain injury. J. Neurotrauma 29 (12), 2209–2219. https://doi.org/10.1089/neu.2011.2274.

Gonzalez-Burgos, I., Rivera-Cervantes, M.C., Velazquez-Zamora, D.A., Feria-Velasco, A., Garcia-Segura, L.M., 2012. Selective estrogen receptor modulators regulate dendritic spine plasticity in the hippocampus of male rats. Neural Plast 2012, 309494. https://doi.org/10.1155/2012/309494.

Gonzalez-Giraldo, Y., Garcia-Segura, L.M., Echeverria, V., Barreto, G.E., 2018. Tibolone preserves mitochondrial functionality and cell morphology in astrocytic cells treated with palmitic acid. Mol. Neurobiol. 55 (5), 4453–4462. https://doi.org/10.1007/s12035-017-0667-3.

Gonzalez, G.A., Hofer, M.P., Syed, Y.A., Amaral, A.I., Rundle, J., Rahman, S., et al., 2016. Tamoxifen accelerates the repair of demyelinated lesions in the central nervous system. Sci. Rep. 6, 31599. https://doi.org/10.1038/srep31599.

Gradinaru, D., Minn, A.L., Artur, Y., Minn, A., Heydel, J.M., 2012. Effect of oxidative stress on UDP-glucuronosyltransferases in rat astrocytes. Toxicol. Lett. 213 (3), 316–324. https://doi.org/10.1016/j.toxlet.2012.07.014.

Gu, X.L., Long, C.X., Sun, L., Xie, C., Lin, X., Cai, H., 2010. Astrocytic expression of Parkinson's disease-related A53T alpha-synuclein causes neurodegeneration in mice. Mol. Brain 3, 12. https://doi.org/10.1186/1756-6606-3-12.

Guzman, C.B., Deighton-Collins, S., Martinez, A., Kleerekoper, M., Zhao, C., Benjamins, J.A., Skafar, D.F., 2005. Activity of estradiol and selective estrogen receptor modulators in the mouse N20.1 oligodendrocyte/astrocytes cell line. Neuro Endocrinol. Lett. 26 (5), 526–532.

Guzman, C.B., Zhao, C., Deighton-Collins, S., Kleerekoper, M., Benjamins, J.A., Skafar, D.F., 2007. Agonist activity of the 3-hydroxy metabolites of tibolone through the oestrogen receptor in the mouse N20.1 oligodendrocyte cell line and normal human astrocytes. J. Neuroendocrinol. 19 (12), 958–965. https://doi.org/10.1111/j.1365-2826.2007.01611.x.

Guzman, S.J., Gerevich, Z., 2016. P2Y receptors in synaptic transmission and plasticity: therapeutic potential in cognitive dysfunction. Neural Plast. 2016, 1207393. https://doi.org/10.1155/2016/1207393.

Hailer, N.P., Wirjatijasa, F., Roser, N., Hischebeth, G.T., Korf, H.W., Dehghani, F., 2001. Astrocytic factors protect neuronal integrity and reduce microglial activation in an in vitro model of N-methyl-D-aspartate-induced excitotoxic injury in organotypic hippocampal slice cultures. Eur. J. Neurosci. 14 (2), 315–326.

Hammond, T.R., Gadea, A., Dupree, J., Kerninon, C., Nait-Oumesmar, B., Aguirre, A., Gallo, V., 2014. Astrocyte-derived endothelin-1 inhibits remyelination through notch activation. Neuron 81 (3), 588–602. https://doi.org/10.1016/j.neuron.2013.11.015.

Hammond, T.R., McEllin, B., Morton, P.D., Raymond, M., Dupree, J., Gallo, V., 2015. Endothelin-B receptor activation in astrocytes regulates the rate of oligodendrocyte regeneration during remyelination. Cell Rep. 13 (10), 2090–2097. https://doi.org/10.1016/j.celrep.2015.11.002.

Han, J., Kesner, P., Metna-Laurent, M., Duan, T., Xu, L., Georges, F., et al., 2012. Acute cannabinoids impair working memory through astroglial CB1 receptor modulation of hippocampal LTD. Cell 148 (5), 1039–1050. https://doi.org/10.1016/j.cell.2012.01.037.

Hargrave, S.L., Davidson, T.L., Zheng, W., Kinzig, K.P., 2016. Western diets induce blood-brain barrier leakage and alter spatial strategies in rats. Behav. Neurosci. 130 (1), 123–135. https://doi.org/10.1037/bne0000110.

Harms, C., Lautenschlager, M., Bergk, A., Katchanov, J., Freyer, D., Kapinya, K., et al., 2001. Differential mechanisms of neuroprotection by 17 beta-estradiol in apoptotic versus necrotic neurodegeneration. J. Neurosci. 21 (8), 2600–2609.

Hasel, P., Dando, O., Jiwaji, Z., Baxter, P., Todd, A.C., Heron, S., et al., 2017. Neurons and neuronal activity control gene expression in astrocytes to regulate their development and metabolism. Nat. Commun. 8, 15132. https://doi.org/10.1038/ncomms15132.

Heringa, M., 2003. Review on raloxifene: profile of a selective estrogen receptor modulator. Int. J. Clin. Pharmacol. Ther. 41 (8), 331–345.

Hidalgo-Lanussa, O., Avila-Rodriguez, M., Baez-Jurado, E., Zamudio, J., Echeverria, V., Garcia-Segura, L.M., Barreto, G.E., 2018. Tibolone reduces oxidative damage and inflammation in microglia stimulated with palmitic acid through mechanisms involving estrogen receptor beta. Mol. Neurobiol. 55 (7), 5462–5477. https://doi.org/10.1007/s12035-017-0777-y.

Hirase, H., Qian, L., Bartho, P., Buzsaki, G., 2004. Calcium dynamics of cortical astrocytic networks in vivo. PLoS Biol. 2 (4), E96. https://doi.org/10.1371/journal.pbio.0020096.

Horgan, K., Cooke, E., Hallett, M.B., Mansel, R.E., 1986. Inhibition of protein kinase C mediated signal transduction by tamoxifen. Importance for antitumour activity. Biochem. Pharmacol. 35 (24), 4463–4465.

Hostenbach, S., D'Haeseleer, M., Kooijman, R., De Keyser, J., 2016. The pathophysiological role of astrocytic endothelin-1. Prog. Neurobiol. 144, 88–102. https://doi.org/10.1016/j.pneurobio.2016.04.009.

Howarth, C., Sutherland, B., Choi, H.B., Martin, C., Lind, B.L., Khennouf, L., et al., 2017. A critical role for astrocytes in hypercapnic vasodilation in brain. J. Neurosci. 37 (9), 2403–2414. https://doi.org/10.1523/JNEUROSCI.0005-16.2016.

Hsu, T.M., Kanoski, S.E., 2014. Blood-brain barrier disruption: mechanistic links between Western diet consumption and dementia. Front. Aging Neurosci. 6, 88. https://doi.org/10.3389/fnagi.2014.00088.

Huang, L., Wu, Z.B., Zhuge, Q., Zheng, W., Shao, B., Wang, B., et al., 2014. Glial scar formation occurs in the human brain after ischemic stroke. Int. J. Med. Sci. 11 (4), 344–348. https://doi.org/10.7150/ijms.8140.

Huerta-Ramos, E., Iniesta, R., Ochoa, S., Cobo, J., Miquel, E., Roca, M., et al., 2014. Effects of raloxifene on cognition in postmenopausal women with schizophrenia: a double-blind, randomized, placebo-controlled trial. Eur. Neuropsychopharmacol. 24 (2), 223–231. https://doi.org/10.1016/j.euroneuro.2013.11.012.

Hyder, A.A., Wunderlich, C.A., Puvanachandra, P., Gururaj, G., Kobusingye, O.C., 2007. The impact of traumatic brain injuries: a global perspective. NeuroRehabilitation 22 (5), 341–353.

Irarrazaval, O.M., 2011. Antagonism of tamoxifen and antidepressants among women with breast cancer. Rev. Med. Chil. 139 (1), 89–99. https://doi.org/10.4067/S0034-98872011000100013.

Ishihara, Y., Itoh, K., Ishida, A., Yamazaki, T., 2015. Selective estrogen-receptor modulators suppress microglial activation and neuronal cell death via an estrogen receptor-dependent pathway. J. Steroid Biochem. Mol. Biol. 145, 85–93. https://doi.org/10.1016/j.jsbmb.2014.10.002.

Ismailoglu, O., Oral, B., Gorgulu, A., Sutcu, R., Demir, N., 2010. Neuroprotective effects of tamoxifen on experimental spinal cord injury in rats. J. Clin. Neurosci. 17 (10), 1306–1310. https://doi.org/10.1016/j.jocn.2010.01.049.

Ismailoglu, O., Oral, B., Sutcu, R., Kara, Y., Tomruk, O., Demir, N., 2013. Neuroprotective effects of raloxifene on experimental spinal cord injury in rats. Am. J. Med. Sci. 345 (1), 39–44. https://doi.org/10.1097/MAJ.0b013e3182522651.

Iusuf, D., Teunissen, S.F., Wagenaar, E., Rosing, H., Beijnen, J.H., Schinkel, A.H., 2011. P-glycoprotein (ABCB1) transports the primary active tamoxifen metabolites endoxifen and 4-hydroxytamoxifen and restricts their brain penetration. J. Pharmacol. Exp. Ther. 337 (3), 710–717. https://doi.org/10.1124/jpet.110.178301.

Jordan, V.C., 2007. New insights into the metabolism of tamoxifen and its role in the treatment and prevention of breast cancer. Steroids 72 (13), 829–842. https://doi.org/10.1016/j.steroids.2007.07.009.

Kanemaru, K., Kubota, J., Sekiya, H., Hirose, K., Okubo, Y., Iino, M., 2013. Calcium-dependent N-cadherin up-regulation mediates reactive astrogliosis and neuroprotection after brain injury. Proc. Natl. Acad. Sci. USA 110 (28), 11612–11617. https://doi.org/10.1073/pnas.1300378110.

Karki, P., Johnson Jr., J., Son, D.S., Aschner, M., Lee, E., 2017. Transcriptional regulation of human transforming growth factor-alpha in astrocytes. Mol. Neurobiol. 54 (2), 964–976. https://doi.org/10.1007/s12035-016-9705-9.

Karki, P., Kim, C., Smith, K., Son, D.S., Aschner, M., Lee, E., 2015. Transcriptional regulation of the astrocytic excitatory amino acid transporter 1 (EAAT1) via NF-kappaB and Yin Yang 1 (YY1). J. Biol. Chem. 290 (39), 23725–23737. https://doi.org/10.1074/jbc.M115.649327.

Karki, P., Smith, K., Johnson Jr., J., Lee, E., 2014a. Astrocyte-derived growth factors and estrogen neuroprotection: role of transforming growth factor-alpha in estrogen-induced upregulation of glutamate transporters in astrocytes. Mol. Cell. Endocrinol. 389 (1–2), 58–64. https://doi.org/10.1016/j.mce.2014.01.010.

Karki, P., Webb, A., Smith, K., Johnson Jr., J., Lee, K., Son, D.S., et al., 2014b. Yin Yang 1 is a repressor of glutamate transporter EAAT2, and it mediates manganese-induced decrease of EAAT2 expression in astrocytes. Mol. Cell. Biol. 34 (7), 1280–1289. https://doi.org/10.1128/MCB.01176-13.

Karki, P., Webb, A., Smith, K., Lee, K., Son, D.S., Aschner, M., Lee, E., 2013. cAMP response element-binding protein (CREB) and nuclear factor kappaB mediate the tamoxifen-induced up-regulation of glutamate transporter 1 (GLT-1) in rat astrocytes. J. Biol. Chem. 288 (40), 28975–28986. https://doi.org/10.1074/jbc.M113.483826.

Karki, P., Webb, A., Zerguine, A., Choi, J., Son, D.S., Lee, E., 2014c. Mechanism of raloxifene-induced upregulation of glutamate transporters in rat primary astrocytes. Glia 62 (8), 1270–1283. https://doi.org/10.1002/glia.22679.

Katayama, T., Kobayashi, H., Okamura, T., Yamasaki-Katayama, Y., Kibayashi, T., Kimura, H., et al., 2012. Accumulating microglia phagocytose injured neurons in hippocampal slice cultures: involvement of p38 MAP kinase. PLoS One 7 (7), e40813. https://doi.org/10.1371/journal.pone.0040813.

Kato, K., Losada-Perez, M., Hidalgo, A., 2018. Gene network underlying the glial regenerative response to central nervous system injury. Dev. Dyn. 247 (1), 85–93. https://doi.org/10.1002/dvdy.24565.

Kelloff, G.J., Malone, W.F., Boone, C.W., Steele, V.E., Doody, L.A., 1992. Intermediate biomarkers of precancer and their application in chemoprevention. J. Cell. Biochem. (Suppl. 16G), 15–21.

Kemp, D.C., Fan, P.W., Stevens, J.C., 2002. Characterization of raloxifene glucuronidation in vitro: contribution of intestinal metabolism to presystemic clearance. Drug Metab. Dispos. 30 (6), 694–700.

Khakh, B.S., McCarthy, K.D., 2015. Astrocyte calcium signaling: from observations to functions and the challenges therein. Cold Spring Harb. Perspect. Biol. 7 (4), a020404. https://doi.org/10.1101/cshperspect.a020404.

Khan, M.M., Wakade, C., de Sevilla, L., Brann, D.W., 2015. Selective estrogen receptor modulators (SERMs) enhance neurogenesis and spine density following focal cerebral ischemia. J. Steroid Biochem. Mol. Biol. 146, 38–47. https://doi.org/10.1016/j.jsbmb.2014.05.001.

Khodabandehloo, F., Hosseini, M., Rajaei, Z., Soukhtanloo, M., Farrokhi, E., Rezaeipour, M., 2013. Brain tissue oxidative damage as a possible mechanism for the deleterious effect of a chronic high dose of estradiol on learning and memory in ovariectomized rats. Arquivos de Neuro-psiquiatria 71 (5), 313–319.

Kierans, A.S., Kirov, I.I., Gonen, O., Haemer, G., Nisenbaum, E., Babb, J.S., et al., 2014. Myoinositol and glutamate complex neurometabolite abnormality after mild traumatic brain injury. Neurology 82 (6), 521–528. https://doi.org/10.1212/WNL.0000000000000105.

Kikuchi, N., Urabe, M., Iwasa, K., Okubo, T., Tsuchiya, H., Hosoda, T., et al., 2000. Atheroprotective effect of estriol and estrone sulfate on human vascular smooth muscle cells. J. Steroid Biochem. Mol. Biol. 72 (1–2), 71–78.

Kim, J.G., Suyama, S., Koch, M., Jin, S., Argente-Arizon, P., Argente, J., et al., 2014. Leptin signaling in astrocytes regulates hypothalamic neuronal circuits and feeding. Nat. Neurosci. 17 (7), 908–910. https://doi.org/10.1038/nn.3725.

Kimelberg, H.K., Jin, Y., Charniga, C., Feustel, P.J., 2003. Neuroprotective activity of tamoxifen in permanent focal ischemia. J. Neurosurgery 99 (1), 138–142.

Komi, J., Lassila, O., 2000. Nonsteroidal anti-estrogens inhibit the functional differentiation of human monocyte-derived dendritic cells. Blood 95 (9), 2875–2882.

Krauser, J.A., Guengerich, F.P., 2005. Cytochrome P450 3A4-catalyzed testosterone 6beta-hydroxylation stereochemistry, kinetic deuterium isotope effects, and rate-limiting steps. J. Biol. Chem. 280 (20), 19496–19506. https://doi.org/10.1074/jbc.M501854200.

Kuo, Y.M., Chen, H.H., Shieh, C.C., Chuang, K.P., Cherng, C.G., Yu, L., 2003. 4-Hydroxytamoxifen attenuates methamphetamine-induced nigrostriatal dopaminergic toxicity in intact and gonadetomized mice. J. Neurochem. 87 (6), 1436–1443.

Lariosa-Willingham, K.D., Rosler, E.S., Tung, J.S., Dugas, J.C., Collins, T.L., Leonoudakis, D., 2016. A high throughput drug screening assay to identify compounds that promote oligodendrocyte differentiation using acutely dissociated and purified oligodendrocyte precursor cells. BMC Res. Notes 9 (1), 419. https://doi.org/10.1186/s13104-016-2220-2.

Lavandera, J., Ruspini, S., Batlle, A., Buzaleh, A.M., 2015. Cytochrome P450 expression in mouse brain: specific isoenzymes involved in Phase I metabolizing system of porphyrinogenic agents in both microsomes and mitochondria. Biochem. Cell. Biol. 93 (1), 102–107. https://doi.org/10.1139/bcb-2014-0088.

LeComte, M.D., Shimada, I.S., Sherwin, C., Spees, J.L., 2015. Notch1-STAT3-ETBR signaling axis controls reactive astrocyte proliferation after brain injury. Proc. Natl. Acad. Sci. USA 112 (28), 8726–8731. https://doi.org/10.1073/pnas.1501029112.

Lee, E., Sidoryk-Wegrzynowicz, M., Wang, N., Webb, A., Son, D.S., Lee, K., Aschner, M., 2012a. GPR30 regulates glutamate transporter GLT-1 expression in rat primary astrocytes. J. Biol. Chem. 287 (32), 26817–26828. https://doi.org/10.1074/jbc.M112.341867.

Lee, E., Sidoryk-Wegrzynowicz, M., Yin, Z., Webb, A., Son, D.S., Aschner, M., 2012b. Transforming growth factor-alpha mediates estrogen-induced upregulation of glutamate transporter GLT-1 in rat primary astrocytes. Glia 60 (7), 1024–1036. https://doi.org/10.1002/glia.22329.

Lee, E.S., Sidoryk, M., Jiang, H., Yin, Z., Aschner, M., 2009. Estrogen and tamoxifen reverse manganese-induced glutamate transporter impairment in astrocytes. J. Neurochem. 110 (2), 530–544. https://doi.org/10.1111/j.1471-4159.2009.06105.x.

Lee, J.-M., Anderson, P.C., Padgitt, J.K., Hanson, J.M., Waters, C.M., Johnson, J.A., 2003. Nrf2, not the estrogen receptor, mediates catechol estrogen-induced activation of the antioxidant responsive element. Biochim. Biophys. Acta (BBA)-Gene Struct. Expr. 1629 (1), 92–101.

Lee, M.L., Martinez-Lozada, Z., Krizman, E.N., Robinson, M.B., 2017. Brain endothelial cells induce astrocytic expression of the glutamate transporter GLT-1 by a Notch-dependent mechanism. J. Neurochem. 143 (5), 489–506. https://doi.org/10.1111/jnc.14135.

Lee, S.G., Su, Z.Z., Emdad, L., Gupta, P., Sarkar, D., Borjabad, A., et al., 2008. Mechanism of ceftriaxone induction of excitatory amino acid transporter-2 expression and glutamate uptake in primary human astrocytes. J. Biol. Chem. 283 (19), 13116–13123. https://doi.org/10.1074/jbc.M707697200.

Legault, C., Maki, P.M., Resnick, S.M., Coker, L., Hogan, P., Bevers, T.B., Shumaker, S.A., 2009. Effects of tamoxifen and raloxifene on memory and other cognitive abilities: cognition in the study of tamoxifen and raloxifene. J. Clin. Oncol. 27 (31), 5144–5152. https://doi.org/10.1200/JCO.2008.21.0716.

Lei, D.-L., Long, J., Hengemihle, J., O'Neill, J., Manaye, K., Ingram, D., Mouton, P., 2003. Effects of estrogen and raloxifene on neuroglia number and morphology in the hippocampus of aged female mice. Neuroscience 121 (3), 659–666.

Li, H., Xie, Y., Zhang, N., Yu, Y., Zhang, Q., Ding, S., 2015. Disruption of IP(3)R2-mediated Ca(2)(+) signaling pathway in astrocytes ameliorates neuronal death and brain damage while reducing behavioral deficits after focal ischemic stroke. Cell Calcium 58 (6), 565–576. https://doi.org/10.1016/j.ceca.2015.09.004.

Li, R., Xu, W., Chen, Y., Qiu, W., Shu, Y., Wu, A., et al., 2014. Raloxifene suppresses experimental autoimmune encephalomyelitis and NF-kappaB-dependent CCL20 expression in reactive astrocytes. PLoS One 9 (4), e94320. https://doi.org/10.1371/journal.pone.0094320.

Li, Y., He, H., Jia, X., Lu, W.L., Lou, J., Wei, Y., 2012. A dual-targeting nanocarrier based on poly(amidoamine) dendrimers conjugated with transferrin and tamoxifen for treating brain gliomas. Biomaterials 33 (15), 3899–3908. https://doi.org/10.1016/j.biomaterials.2012.02.004.

Lien, E.A., Wester, K., Lonning, P.E., Solheim, E., Ueland, P.M., 1991. Distribution of tamoxifen and metabolites into brain tissue and brain metastases in breast cancer patients. Br. J. Cancer 63 (4), 641–645.

Lim, S.H., Park, E., You, B., Jung, Y., Park, A.R., Park, S.G., Lee, J.R., 2013. Neuronal synapse formation induced by microglia and interleukin 10. PLoS One 8 (11), e81218. https://doi.org/10.1371/journal.pone.0081218.

Lin, J., Cai, W., 2004. Effect of vimentin on reactive gliosis: in vitro and in vivo analysis. J. Neurotrauma 21 (11), 1671–1682. https://doi.org/10.1089/neu.2004.21.1671.

Liu, H.Y., Buenafe, A.C., Matejuk, A., Ito, A., Zamora, A., Dwyer, J., et al., 2002. Estrogen inhibition of EAE involves effects on dendritic cell function. J. Neurosci. Res. 70 (2), 238–248. https://doi.org/10.1002/jnr.10409.

Liu, Y., Huang, L., Guan, X., Li, H., Zhang, Q.Q., Han, C., et al., 2016. ER-alpha36, a novel variant of ERalpha, is involved in the regulation of Tamoxifen-sensitivity of glioblastoma cells. Steroids 111, 127–133. https://doi.org/10.1016/j.steroids.2016.02.009.

Loov, C., Hillered, L., Ebendal, T., Erlandsson, A., 2012. Engulfing astrocytes protect neurons from contact-induced apoptosis following injury. PLoS One 7 (3), e33090. https://doi.org/10.1371/journal.pone.0033090.

Lopez Rodriguez, A.B., Mateos Vicente, B., Romero-Zerbo, S.Y., Rodriguez-Rodriguez, N., Bellini, M.J., Rodriguez de Fonseca, F., et al., 2011. Estradiol decreases cortical reactive astrogliosis after brain injury by a mechanism involving cannabinoid receptors. Cereb. Cortex 21 (9), 2046–2055. https://doi.org/10.1093/cercor/bhq277.

Lu, C.L., Herndon, C., 2017. New roles for neuronal estrogen receptors. Neurogastroenterol. Motil. 29 (7). https://doi.org/10.1111/nmo.13121.

Maggioli, E., McArthur, S., Mauro, C., Kieswich, J., Kusters, D.H., Reutelingsperger, C.P., et al., 2016. Estrogen protects the blood-brain barrier from inflammation-induced disruption and increased lymphocyte trafficking. Brain Behav. Immun. 51, 212–222. https://doi.org/10.1016/j.bbi.2015.08.020.

Magnus, T., Chan, A., Linker, R.A., Toyka, K.V., Gold, R., 2002. Astrocytes are less efficient in the removal of apoptotic lymphocytes than microglia cells: implications for the role of glial cells in the inflamed central nervous system. J. Neuropathol. Exp. Neurol. 61 (9), 760–766.

Malaplate-Armand, C., Ferrari, L., Masson, C., Visvikis-Siest, S., Lambert, H., Batt, A.M., 2005. Down-regulation of astroglial CYP2C, glucocorticoid receptor and constitutive androstane receptor genes in response to cocaine in human U373 MG astrocytoma cells. Toxicol. Lett. 159 (3), 203–211. https://doi.org/10.1016/j.toxlet.2005.04.005.

Mann, A., Miksys, S.L., Gaedigk, A., Kish, S.J., Mash, D.C., Tyndale, R.F., 2012. The neuroprotective enzyme CYP2D6 increases in the brain with age and is lower in Parkinson's disease patients. Neurobiol. Aging 33 (9), 2160–2171. https://doi.org/10.1016/j.neurobiolaging.2011.08.014.

Mann, A., Tyndale, R.F., 2010. Cytochrome P450 2D6 enzyme neuroprotects against 1-methyl-4-phenylpyridinium toxicity in SH-SY5Y neuronal cells. Eur. J. Neurosci. 31 (7), 1185–1193. https://doi.org/10.1111/j.1460-9568.2010.07142.x.

Mar, J., Arrospide, A., Begiristain, J.M., Larranaga, I., Elosegui, E., Oliva-Moreno, J., 2011. The impact of acquired brain damage in terms of epidemiology, economics and loss in quality of life. BMC Neurol. 11, 46. https://doi.org/10.1186/1471-2377-11-46.

Martineau, M., 2013. Gliotransmission: focus on exocytotic release of L-glutamate and D-serine from astrocytes. Biochem. Soc. Trans. 41 (6), 1557–1561. https://doi.org/10.1042/BST20130195.

Matsuda, T., Nakamura, T., Nakao, K., Arai, T., Katsuki, M., Heike, T., Yokota, T., 1999. STAT3 activation is sufficient to maintain an undifferentiated state of mouse embryonic stem cells. EMBO J. 18 (15), 4261–4269. https://doi.org/10.1093/emboj/18.15.4261.

Mattison, H.A., Nie, H., Gao, H., Zhou, H., Hong, J.S., Zhang, J., 2013. Suppressed pro-inflammatory response of microglia in CX3CR1 knockout mice. J. Neuroimmunol. 257 (1–2), 110–115. https://doi.org/10.1016/j.jneuroim.2013.02.008.

Matyskova, R., Zelezna, B., Maixnerova, J., Koutova, D., Haluzik, M., Maletinska, L., 2010. Estradiol supplementation helps overcome central leptin resistance of ovariectomized mice on a high fat diet. Horm. Metab. Res. 42 (3), 182–186. https://doi.org/10.1055/s-0029-1243250.

Mauvais-Jarvis, F., Clegg, D.J., Hevener, A.L., 2013. The role of estrogens in control of energy balance and glucose homeostasis. Endocr. Rev. 34 (3), 309–338. https://doi.org/10.1210/er.2012-1055.

McLellan, M.A., Rosenthal, N.A., Pinto, A.R., 2017. Cre-loxP-mediated recombination: general principles and experimental considerations. Curr. Protoc. Mouse Biol. 7 (1), 1–12. https://doi.org/10.1002/cpmo.22.

Meyer, R.P., Knoth, R., Schiltz, E., Volk, B., 2001. Possible function of astrocyte cytochrome P450 in control of xenobiotic phenytoin in the brain: in vitro studies on murine astrocyte primary cultures. Exp. Neurol. 167 (2), 376–384. https://doi.org/10.1006/exnr.2000.7553.

Miksys, S., Hoffmann, E., Tyndale, R.F., 2000. Regional and cellular induction of nicotine-metabolizing CYP2B1 in rat brain by chronic nicotine treatment. Biochem. Pharmacol. 59 (12), 1501–1511.

Miksys, S., Lerman, C., Shields, P.G., Mash, D.C., Tyndale, R.F., 2003. Smoking, alcoholism and genetic polymorphisms alter CYP2B6 levels in human brain. Neuropharmacology 45 (1), 122–132.

Miksys, S., Rao, Y., Hoffmann, E., Mash, D.C., Tyndale, R.F., 2002. Regional and cellular expression of CYP2D6 in human brain: higher levels in alcoholics. J. Neurochem. 82 (6), 1376–1387.

Miksys, S., Tyndale, R.F., 2004. The unique regulation of brain cytochrome P450 2 (CYP2) family enzymes by drugs and genetics. Drug Metab. Rev. 36 (2), 313–333. https://doi.org/10.1081/DMR-120034149.

Milatovic, D., Yin, Z., Gupta, R.C., Sidoryk, M., Albrecht, J., Aschner, J.L., Aschner, M., 2007. Manganese induces oxidative impairment in cultured rat astrocytes. Toxicol. Sci. 98 (1), 198–205. https://doi.org/10.1093/toxsci/kfm095.

Mitra, S., Ghosh, N., Sinha, P., Chakrabarti, N., Bhattacharyya, A., 2015. Alteration in Nuclear Factor-KappaB pathway and functionality of estrogen via receptors promote neuroinflammation in frontal cortex after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine treatment. Sci. Rep. 5, 13949. https://doi.org/10.1038/srep13949.

Mo, Z., Liu, M., Yang, F., Luo, H., Li, Z., Tu, G., Yang, G., 2013. GPR30 as an initiator of tamoxifen resistance in hormone-dependent breast cancer. Breast Cancer Res. 15 (6), R114. https://doi.org/10.1186/bcr3581.

Montine, T.J., Quinn, J.F., Milatovic, D., Silbert, L.C., Dang, T., Sanchez, S., et al., 2002. Peripheral F2-isoprostanes and F4-neuroprostanes are not increased in Alzheimer's disease. Ann. Neurol. 52 (2), 175–179. https://doi.org/10.1002/ana.10272.

Moreira, P.I., Custodio, J.B., Oliveira, C.R., Santos, M.S., 2004. Hydroxytamoxifen protects against oxidative stress in brain mitochondria. Biochem. Pharmacol. 68 (1), 195–204. https://doi.org/10.1016/j.bcp.2004.03.019.

Moreira, P.I., Custodio, J.B., Oliveira, C.R., Santos, M.S., 2005. Brain mitochondrial injury induced by oxidative stress-related events is prevented by tamoxifen. Neuropharmacology 48 (3), 435–447. https://doi.org/10.1016/j.neuropharm.2004.10.012.

Mosquera, L., Colon, J.M., Santiago, J.M., Torrado, A.I., Melendez, M., Segarra, A.C., et al., 2014. Tamoxifen and estradiol improved locomotor function and increased spared tissue in rats after spinal cord injury: their antioxidant effect and role of estrogen receptor alpha. Brain Res. 1561, 11–22. https://doi.org/10.1016/j.brainres.2014.03.002.

Mukai, H., Kimoto, T., Hojo, Y., Kawato, S., Murakami, G., Higo, S., et al., 2010. Modulation of synaptic plasticity by brain estrogen in the hippocampus. Biochim. Biophys. Acta 1800 (10), 1030–1044. https://doi.org/10.1016/j.bbagen.2009.11.002.

Nair, A., Frederick, T.J., Miller, S.D., 2008. Astrocytes in multiple sclerosis: a product of their environment. Cell. Mol. Life Sci. 65 (17), 2702–2720. https://doi.org/10.1007/s00018-008-8059-5.

Naud, J., Harding, J., Lamarche, C., Beauchemin, S., Leblond, F.A., Pichette, V., 2016. Effects of chronic renal failure on brain cytochrome P450 in rats. Drug Metab. Dispos. 44 (8), 1174–1179. https://doi.org/10.1124/dmd.116.070052.

Navarrete, M., Araque, A., 2008. Endocannabinoids mediate neuron-astrocyte communication. Neuron 57 (6), 883–893. https://doi.org/10.1016/j.neuron.2008.01.029.

Neary, J.T., Kang, Y., Willoughby, K.A., Ellis, E.F., 2003. Activation of extracellular signal-regulated kinase by stretch-induced injury in astrocytes involves extracellular ATP and P2 purinergic receptors. J Neurosci 23 (6), 2348–2356.

Nebert, D.W., Wikvall, K., Miller, W.L., 2013. Human cytochromes P450 in health and disease. Philos. Trans. R Soc. Lond. B Biol. Sci. 368 (1612), 20120431. https://doi.org/10.1098/rstb.2012.0431.

Neele, S.J., Rombouts, S.A., Bierlaagh, M.A., Barkhof, F., Scheltens, P., Netelenbos, J.C., 2001. Raloxifene affects brain activation patterns in postmenopausal women during visual encoding. J. Clin. Endocrinol. Metab. 86 (3), 1422–1424. https://doi.org/10.1210/jcem.86.3.7454.

Neven, P., Jongen, L., Lintermans, A., Van Asten, K., Blomme, C., Lambrechts, D., et al., 2018. Tamoxifen metabolism and efficacy in breast cancer- a prospective multicentre trial. Clin. Cancer Res. https://doi.org/10.1158/1078-0432.CCR-17-3028.

Newhouse, P., Albert, K., Astur, R., Johnson, J., Naylor, M., Dumas, J., 2013. Tamoxifen improves cholinergically modulated cognitive performance in postmenopausal women. Neuropsychopharmacology 38 (13), 2632–2643. https://doi.org/10.1038/npp.2013.172.

O'neill, K., Chen, S., Brinton, R.D., 2004. Impact of the selective estrogen receptor modulator, raloxifene, on neuronal survival and outgrowth following toxic insults associated with aging and Alzheimer's disease. Exp. Neurol. 185 (1), 63–80.

Ohashi, K., Yamazaki, T., Kitamura, S., Ohta, S., Izumi, S., Kominami, S., 2007. Allosteric inhibition of rat neuronal nitric-oxide synthase caused by interference with the binding of calmodulin to the enzyme. Biochim. Biophys. Acta 1770 (2), 231–240. https://doi.org/10.1016/j.bbagen.2006.10.002.

Okada, M., Makino, A., Nakajima, M., Okuyama, S., Furukawa, S., Furukawa, Y., 2010. Estrogen stimulates proliferation and differentiation of neural stem/progenitor cells through different signal transduction pathways. Int. J. Mol. Sci. 11 (10), 4114–4123. https://doi.org/10.3390/ijms11104114.

Ostrow, L.W., Suchyna, T.M., Sachs, F., 2011. Stretch induced endothelin-1 secretion by adult rat astrocytes involves calcium influx via stretch-activated ion channels (SACs). Biochem. Biophys. Res. Commun. 410 (1), 81–86. https://doi.org/10.1016/j.bbrc.2011.05.109.

Osuka, K., Feustel, P.J., Mongin, A.A., Tranmer, B.I., Kimelberg, H.K., 2001. Tamoxifen inhibits nitrotyrosine formation after reversible middle cerebral artery occlusion in the rat. J. Neurochem. 76 (6), 1842–1850.

Ouzzine, M., Gulberti, S., Ramalanjaona, N., Magdalou, J., Fournel-Gigleux, S., 2014. The UDP-glucuronosyltransferases of the blood-brain barrier: their role in drug metabolism and detoxication. Front. Cell. Neurosci. 8, 349. https://doi.org/10.3389/fncel.2014.00349.

Padmashri, R., Suresh, A., Boska, M.D., Dunaevsky, A., 2015. Motor-skill learning is dependent on astrocytic activity. Neural. Plast. 2015, 938023. https://doi.org/10.1155/2015/938023.

Paech, K., Webb, P., Kuiper, G.G., Nilsson, S., Gustafsson, J.-Å., Kushner, P.J., Scanlan, T.S., 1997. Differential ligand activation of estrogen receptors ERα and ERβ at AP1 sites. Science 277 (5331), 1508–1510.

Pak, T.R., Chung, W.C., Lund, T.D., Hinds, L.R., Clay, C.M., Handa, R.J., 2005. The androgen metabolite, 5alpha-androstane-3beta, 17beta-diol, is a potent modulator of estrogen receptor-beta1-mediated gene transcription in neuronal cells. Endocrinology 146 (1), 147–155. https://doi.org/10.1210/en.2004-0871.

Park, L.C., Zhang, H., Gibson, G.E., 2001. Co-culture with astrocytes or microglia protects metabolically impaired neurons. Mech. Ageing Dev. 123 (1), 21–27.

Pasti, L., Pozzan, T., Carmignoto, G., 1995. Long-lasting changes of calcium oscillations in astrocytes A new form of glutamate-mediated plasticity. J. Biol. Chem. 270 (25), 15203–15210.

Pekny, M., Pekna, M., 2014. Astrocyte reactivity and reactive astrogliosis: costs and benefits. Physiol. Rev. 94 (4), 1077–1098. https://doi.org/10.1152/physrev.00041.2013.

Peng, J., Sengupta, S., Jordan, V.C., 2009. Potential of selective estrogen receptor modulators as treatments and preventives of breast cancer. Anticancer Agents Med. Chem. 9 (5), 481–499.

Perkins, M.S., Louw-du Toit, R., Africander, D., 2018. Hormone therapy and breast cancer: emerging steroid receptor mechanisms. J. Mol. Endocrinol. https://doi.org/10.1530/JME-18-0094.

Perry, R.R., Kang, Y., Greaves, B.R., 1995. Relationship between tamoxifen-induced transforming growth factor beta 1 expression, cytostasis and apoptosis in human breast cancer cells. Br. J. Cancer 72 (6), 1441–1446.

Pfaffl, M.W., Lange, I.G., Daxenberger, A., Meyer, H.H., 2001. Tissue-specific expression pattern of estrogen receptors (ER): quantification of ER alpha and ER beta mRNA with real-time RT-PCR. APMIS 109 (5), 345–355.

Pinto-Almazan, R., Rivas-Arancibia, S., Farfan-Garcia, E.D., Rodriguez-Martinez, E., Guerra-Araiza, C., 2014. Neuroprotective effects of tibolone against oxidative stress induced by ozone exposure. Rev. Neurol. 58 (10), 441–448.

Pinto-Basto, D., Silva, J.P., Queiroz, M.J., Moreno, A.J., Coutinho, O.P., 2009. Antioxidant activity of synthetic diarylamines: a mitochondrial and cellular approach. Mitochondrion 9 (1), 17–26. https://doi.org/10.1016/j.mito.2008.10.001.

Pluta, R., Furmaga-Jablonska, W., Maciejewski, R., Ulamek-Koziol, M., Jablonski, M., 2013. Brain ischemia activates beta- and gamma-secretase cleavage of amyloid precursor protein: significance in sporadic Alzheimer's disease. Mol. Neurobiol. 47 (1), 425–434. https://doi.org/10.1007/s12035-012-8360-z.

Polavarapu, R., An, J., Zhang, C., Yepes, M., 2008. Regulated intramembrane proteolysis of the low-density lipoprotein receptor-related protein mediates ischemic cell death. Am. J. Pathol. 172 (5), 1355–1362. https://doi.org/10.2353/ajpath.2008.070975.

Polo-Kantola, P., Portin, R., Polo, O., Helenius, H., Irjala, K., Erkkola, R., 1998. The effect of short-term estrogen replacement therapy on cognition: a randomized, double-blind, cross-over trial in postmenopausal women. Obstet. Gynecol. 91 (3), 459–466.

Qiu, J., Bosch, M.A., Tobias, S.C., Grandy, D.K., Scanlan, T.S., Ronnekleiv, O.K., Kelly, M.J., 2003. Rapid signaling of estrogen in hypothalamic neurons involves a novel G-protein-coupled estrogen receptor that activates protein kinase C. J. Neurosci. 23 (29), 9529–9540.

Ray, M.K., Fagan, S.P., Brunicardi, F.C., 2000. The Cre-loxP system: a versatile tool for targeting genes in a cell- and stage-specific manner. Cell Transplant 9 (6), 805–815.

Reddel, R.R., Murphy, L.C., Sutherland, R.L., 1983. Effects of biologically active metabolites of tamoxifen on the proliferation kinetics of MCF-7 human breast cancer cells in vitro. Cancer Res. 43 (10), 4618–4624.

Renodon, A., Boucher, J.-L., Sari, M.-A., Delaforge, M., Ouazzani, J., Mansuy, D., 1997. Strong inhibition of neuronal nitric oxide synthase by the calmodulin antagonist and anti-estrogen drug tamoxifen. Biochem. Pharmacol. 54 (10), 1109–1114.

Rivera, P., Perez-Martin, M., Pavon, F.J., Serrano, A., Crespillo, A., Cifuentes, M., et al., 2013. Pharmacological administration of the isoflavone daidzein enhances cell proliferation and reduces high fat diet-induced apoptosis and gliosis in the rat hippocampus. PLoS One 8 (5), e64750. https://doi.org/10.1371/journal.pone.0064750.

Romine, J., Gao, X., Xu, X.M., So, K.F., Chen, J., 2015. The proliferation of amplifying neural progenitor cells is impaired in the aging brain and restored by the mTOR pathway activation. Neurobiol. Aging 36 (4), 1716–1726. https://doi.org/10.1016/j.neurobiolaging.2015.01.003.

Rosenbrock, H., Hagemeyer, C., Singec, I., Knoth, R., Volk, B., 1999. Testosterone metabolism in rat brain is differentially enhanced by phenytoin-inducible cytochrome P450 isoforms. J. Neuroendocrinol. 11 (8), 597–604.

Rosito, M., Lauro, C., Chece, G., Porzia, A., Monaco, L., Mainiero, F., et al., 2014. Trasmembrane chemokines CX3CL1 and CXCL16 drive interplay between neurons, microglia and astrocytes to counteract pMCAO and excitotoxic neuronal death. Front. Cell. Neurosci. 8, 193. https://doi.org/10.3389/fncel.2014.00193.

Russo, J., Russo, I.H., 2006. The role of estrogen in the initiation of breast cancer. J. Steroid Biochem. Mol. Biol. 102 (1–5), 89–96. https://doi.org/10.1016/j.jsbmb.2006.09.004.

Rutanen, E.M., Heikkinen, J., Halonen, K., Komi, J., Lammintausta, R., Ylikorkala, O., 2003. Effects of ospemifene, a novel SERM, on hormones, genital tract, climacteric symptoms, and quality of life in postmenopausal women: a double-blind, randomized trial. Menopause 10 (5), 433–439. https://doi.org/10.1097/01.GME.0000063609.62485.27.

Rzemieniec, J., Litwa, E., Wnuk, A., Lason, W., Golas, A., Krzeptowski, W., Kajta, M., 2015. Neuroprotective action of raloxifene against hypoxia-induced damage in mouse hippocampal cells depends on ERalpha but not ERbeta or GPR30 signalling. J. Steroid Biochem. Mol. Biol. 146, 26–37. https://doi.org/10.1016/j.jsbmb.2014.05.005.

Sadarangani, A., Salgado, A.M., Kato, S., Pinto, M., Carvajal, A., Monso, C., et al., 2005. In vivo and in vitro estrogenic and progestagenic actions of Tibolone. Biol. Res. 38 (2–3), 245–258.

Saladores, P., Murdter, T., Eccles, D., Chowbay, B., Zgheib, N.K., Winter, S., et al., 2015. Tamoxifen metabolism predicts drug concentrations and outcome in premenopausal patients with early breast cancer. Pharmacogenomics J. 15 (1), 84–94. https://doi.org/10.1038/tpj.2014.34.

Sanders, J., Cowansage, K., Baumgartel, K., Mayford, M., 2012. Elimination of dendritic spines with long-term memory is specific to active circuits. J. Neurosci. 32 (36), 12570–12578. https://doi.org/10.1523/JNEUROSCI.1131-12.2012.

Sauer, B., 1998. Inducible gene targeting in mice using the Cre/lox system. Methods 14 (4), 381–392. https://doi.org/10.1006/meth.1998.0593.

Schiff, R., Reddy, P., Ahotupa, M., Coronado-Heinsohn, E., Grim, M., Hilsenbeck, S.G., et al., 2000. Oxidative stress and AP-1 activity in tamoxifen-resistant breast tumors in vivo. J. Natl. Cancer Inst. 92 (23), 1926–1934.

Sharma, K., Mehra, R.D., 2008. Long-term administration of estrogen or tamoxifen to ovariectomized rats affords neuroprotection to hippocampal neurons by modulating the expression of Bcl-2 and Bax. Brain Res. 1204, 1–15. https://doi.org/10.1016/j.brainres.2008.01.080.

Shaywitz, S.E., Shaywitz, B.A., Pugh, K.R., Fulbright, R.K., Skudlarski, P., Mencl, W.E., et al., 1999. Effect of estrogen on brain activation patterns in postmenopausal women during working memory tasks. JAMA 281 (13), 1197–1202.

Sheng, W.S., Hu, S., Feng, A., Rock, R.B., 2013. Reactive oxygen species from human astrocytes induced functional impairment and oxidative damage. Neurochem. Res. 38 (10), 2148–2159. https://doi.org/10.1007/s11064-013-1123-z.

Shigetomi, E., Bushong, E.A., Haustein, M.D., Tong, X., Jackson-Weaver, O., Kracun, S., et al., 2013a. Imaging calcium microdomains within entire astrocyte territories and endfeet with GCaMPs expressed using adeno-associated viruses. J. Gen. Physiol. 141 (5), 633–647. https://doi.org/10.1085/jgp.201210949.

Shigetomi, E., Jackson-Weaver, O., Huckstepp, R.T., O'Dell, T.J., Khakh, B.S., 2013b. TRPA1 channels are regulators of astrocyte basal calcium levels and long-term potentiation via constitutive D-serine release. J. Neurosci. 33 (24), 10143–10153. https://doi.org/10.1523/JNEUROSCI.5779-12.2013.

Shimada, I.S., Borders, A., Aronshtam, A., Spees, J.L., 2011. Proliferating reactive astrocytes are regulated by Notch-1 in the peri-infarct area after stroke. Stroke 42 (11), 3231–3237. https://doi.org/10.1161/STROKEAHA.111.623280.

Shinozaki, Y., Shibata, K., Yoshida, K., Shigetomi, E., Gachet, C., Ikenaka, K., et al., 2017. Transformation of astrocytes to a neuroprotective phenotype by microglia via P2Y1 receptor downregulation. Cell Rep. 19 (6), 1151–1164. https://doi.org/10.1016/j.celrep.2017.04.047.

Singh, M.S., Francis, P.A., Michael, M., 2011. Tamoxifen, cytochrome P450 genes and breast cancer clinical outcomes. Breast 20 (2), 111–118. https://doi.org/10.1016/j.breast.2010.11.003.

Sirko, S., Behrendt, G., Johansson, P.A., Tripathi, P., Costa, M., Bek, S., et al., 2013. Reactive glia in the injured brain acquire stem cell properties in response to sonic hedgehog. [corrected]. Cell Stem Cell 12 (4), 426–439. https://doi.org/10.1016/j.stem.2013.01.019.

Slezak, M., Goritz, C., Niemiec, A., Frisen, J., Chambon, P., Metzger, D., Pfrieger, F.W., 2007. Transgenic mice for conditional gene manipulation in astroglial cells. Glia 55 (15), 1565–1576. https://doi.org/10.1002/glia.20570.

Sofroniew, M.V., Vinters, H.V., 2010. Astrocytes: biology and pathology. Acta Neuropathol. 119 (1), 7–35. https://doi.org/10.1007/s00401-009-0619-8.

Suh, H., Consiglio, A., Ray, J., Sawai, T., D'Amour, K.A., Gage, F.H., 2007. In vivo fate analysis reveals the multipotent and self-renewal capacities of Sox2+ neural stem cells in the adult hippocampus. Cell Stem Cell 1 (5), 515–528. https://doi.org/10.1016/j.stem.2007.09.002.

Suleman, F.G., Abid, A., Gradinaru, D., Daval, J.L., Magdalou, J., Minn, A., 1998. Identification of the uridine diphosphate glucuronosyltransferase isoform UGT1A6 in rat brain and in primary cultures of neurons and astrocytes. Arch. Biochem. Biophys. 358 (1), 63–67. https://doi.org/10.1006/abbi.1998.0842.

Sun, D., Jones, N.R., Manni, A., Lazarus, P., 2013a. Characterization of raloxifene glucuronidation: potential role of UGT1A8 genotype on raloxifene metabolism in vivo. Cancer Prev. Res. (Phila) 6 (7), 719–730. https://doi.org/10.1158/1940-6207.CAPR-12-0448.

Sun, X., Ji, C., Hu, T., Wang, Z., Chen, G., 2013b. Tamoxifen as an effective neuroprotectant against early brain injury and learning deficits induced by subarachnoid hemorrhage: possible involvement of inflammatory signaling. J. Neuroinflammation 10, 157. https://doi.org/10.1186/1742-2094-10-157.

Suuronen, T., Nuutinen, T., Huuskonen, J., Ojala, J., Thornell, A., Salminen, A., 2005. Anti-inflammatory effect of selective estrogen receptor modulators (SERMs) in microglial cells. Inflamm. Res. 54 (5), 194–203. https://doi.org/10.1007/s00011-005-1343-z.

Szalay, G., Martinecz, B., Lenart, N., Kornyei, Z., Orsolits, B., Judak, L., et al., 2016. Microglia protect against brain injury and their selective elimination dysregulates neuronal network activity after stroke. Nat. Commun. 7, 11499. https://doi.org/10.1038/ncomms11499.

Szamel, I., Hindy, I., Budai, B., Kangas, L., Hajba, A., Lammintausta, R., 1998. Endocrine mechanism of action of toremifene at the level of the central nervous system in advanced breast cancer patients. Cancer Chemother. Pharmacol. 42 (3), 241–246. https://doi.org/10.1007/s002800050811.

Tang, H., Zhang, Q., Yang, L., Dong, Y., Khan, M., Yang, F., et al., 2014. GPR30 mediates estrogen rapid signaling and neuroprotection. Mol. Cell. Endocrinol. 387 (1–2), 52–58. https://doi.org/10.1016/j.mce.2014.01.024.

Teft, W.A., Mansell, S.E., Kim, R.B., 2011. Endoxifen, the active metabolite of tamoxifen, is a substrate of the efflux transporter P-glycoprotein (multidrug resistance 1). Drug Metab. Dispos. 39 (3), 558–562. https://doi.org/10.1124/dmd.110.036160.

Terashvili, M., Sarkar, P., Nostrand, M.V., Falck, J.R., Harder, D.R., 2012. The protective effect of astrocyte-derived 14,15-epoxyeicosatrienoic acid on hydrogen peroxide-induced cell injury in astrocyte-dopaminergic neuronal cell line co-culture. Neuroscience 223, 68–76. https://doi.org/10.1016/j.neuroscience.2012.07.045.

Tian, D.S., Liu, J.L., Xie, M.J., Zhan, Y., Qu, W.S., Yu, Z.Y., et al., 2009. Tamoxifen attenuates inflammatory-mediated damage and improves functional outcome after spinal cord injury in rats. J. Neurochem. 109 (6), 1658–1667. https://doi.org/10.1111/j.1471-4159.2009.06077.x.

Tian, J.M., Ran, B., Zhang, C.L., Yan, D.M., Li, X.H., 2018. Estrogen and progesterone promote breast cancer cell proliferation by inducing cyclin G1 expression. Braz. J. Med. Biol. Res. 51 (3), 1–7. https://doi.org/10.1590/1414-431X20175612.

Tiffany-Castiglioni, E., Hong, S., Qian, Y., 2011. Copper handling by astrocytes: insights into neurodegenerative diseases. Int. J. Dev. Neurosci. 29 (8), 811–818. https://doi.org/10.1016/j.ijdevneu.2011.09.004.

Tindberg, N., Baldwin, H.A., Cross, A.J., Ingelman-Sundberg, M., 1996. Induction of cytochrome P450 2E1 expression in rat and gerbil astrocytes by inflammatory factors and ischemic injury. Mol. Pharmacol. 50 (5), 1065–1072.

Toro-Urrego, N., Garcia-Segura, L.M., Echeverria, V., Barreto, G.E., 2016. Testosterone protects mitochondrial function and regulates neuroglobin expression in astrocytic cells exposed to glucose deprivation. Front. Aging Neurosci. 8, 152. https://doi.org/10.3389/fnagi.2016.00152.

Trevino, L.S., Wang, Q., Walker, C.L., 2015. Hypothesis: activation of rapid signaling by environmental estrogens and epigenetic reprogramming in breast cancer. Reprod. Toxicol. 54, 136–140. https://doi.org/10.1016/j.reprotox.2014.12.014.

Tsai, Y.T., Wang, C.C., Leung, P.O., Lin, K.C., Chio, C.C., Hu, C.Y., Kuo, J.R., 2014. Extracellular signal-regulated kinase 1/2 is involved in a tamoxifen neuroprotective effect in a lateral fluid percussion injury rat model. J. Surg. Res. 189 (1), 106–116. https://doi.org/10.1016/j.jss.2014.02.009.

Tyler, W.A., Gangoli, N., Gokina, P., Kim, H.A., Covey, M., Levison, S.W., Wood, T.L., 2009. Activation of the mammalian target of rapamycin (mTOR) is essential for oligodendrocyte differentiation. J. Neurosci. 29 (19), 6367–6378. https://doi.org/10.1523/JNEUROSCI.0234-09.2009.

Valny, M., Honsa, P., Kirdajova, D., Kamenik, Z., Anderova, M., 2016. Tamoxifen in the mouse brain: implications for fate-mapping studies using the tamoxifen-inducible Cre-loxP system. Front. Cell. Neurosci. 10, 243. https://doi.org/10.3389/fncel.2016.00243.

Valles, S.L., Dolz-Gaiton, P., Gambini, J., Borras, C., Lloret, A., Pallardo, F.V., Vina, J., 2010. Estradiol or genistein prevent Alzheimer's disease-associated inflammation correlating with an increase PPAR gamma expression in cultured astrocytes. Brain Res. 1312, 138–144. https://doi.org/10.1016/j.brainres.2009.11.044.

van Niekerk, E.A., Tuszynski, M.H., Lu, P., Dulin, J.N., 2016. Molecular and cellular mechanisms of axonal regeneration after spinal cord injury. Mol. Cell. Proteom. 15 (2), 394–408. https://doi.org/10.1074/mcp.R115.053751.

Villa, A., Vegeto, E., Poletti, A., Maggi, A., 2016. Estrogens, neuroinflammation, and neurodegeneration. Endocr. Rev. 37 (4), 372–402. https://doi.org/10.1210/er.2016-1007.

Voevodskaya, O., Sundgren, P.C., Strandberg, O., Zetterberg, H., Minthon, L., Blennow, K., et al., 2016. Myo-inositol changes precede amyloid pathology and relate to APOE genotype in Alzheimer disease. Neurology 86 (19), 1754–1761. https://doi.org/10.1212/WNL.0000000000002672.

Wakade, C., Khan, M.M., De Sevilla, L.M., Zhang, Q.G., Mahesh, V.B., Brann, D.W., 2008. Tamoxifen neuroprotection in cerebral ischemia involves attenuation of kinase activation and superoxide production and potentiation of mitochondrial superoxide dismutase. Endocrinology 149 (1), 367–379. https://doi.org/10.1210/en.2007-0899.

Wang, C.-C., Wee, H.-Y., Chio, C.-C., Hu, C.-Y., Kuo, J.-R., 2016a. Effects of tamoxifen on traumatic brain injury-induced depression in male rats. Formosan J. Surgery 49 (3), 101–109.

Wang, J.M., Liu, L., Brinton, R.D., 2008. Estradiol-17beta-induced human neural progenitor cell proliferation is mediated by an estrogen receptor beta-phosphorylated extracellularly regulated kinase pathway. Endocrinology 149 (1), 208–218. https://doi.org/10.1210/en.2007-1155.

Wang, X., Seekaew, P., Gao, X., Chen, J., 2016b. Traumatic brain injury stimulates neural stem cell proliferation via mammalian target of rapamycin signaling pathway activation. eNeuro 3 (5). https://doi.org/10.1523/ENEURO.0162-16.2016.

Webb, P., Lopez, G.N., Uht, R.M., Kushner, P.J., 1995. Tamoxifen activation of the estrogen receptor/AP-1 pathway: potential origin for the cell-specific estrogen-like effects of antiestrogens. Mol. Endocrinol. 9 (4), 443–456. https://doi.org/10.1210/mend.9.4.7659088.

Wegman, P., Elingarami, S., Carstensen, J., Stål, O., Nordenskjöld, B., Wingren, S., 2007. Genetic variants of CYP3A5, CYP2D6, SULT1A1, UGT2B15 and tamoxifen response in postmenopausal patients with breast cancer. Breast Cancer Res. 9 (1), R7.

Wei, H.Y., Ma, X., 2014. Tamoxifen reduces infiltration of inflammatory cells, apoptosis and inhibits IKK/NF-kB pathway after spinal cord injury in rats. Neurol. Sci. 35 (11), 1763–1768. https://doi.org/10.1007/s10072-014-1828-z.

Weickert, T.W., Weinberg, D., Lenroot, R., Catts, S.V., Wells, R., Vercammen, A., et al., 2015. Adjunctive raloxifene treatment improves attention and memory in men and women with schizophrenia. Mol. Psych. 20 (6), 685–694. https://doi.org/10.1038/mp.2015.11.

White, I., 2003. Tamoxifen: is it safe? Comparison of activation and detoxication mechanisms in rodents and in humans. Curr. Drug Metab. 4 (3), 223–239.

Wolfe, M.S., 2008. Gamma-secretase inhibition and modulation for Alzheimer's disease. Curr. Alzheimer Res. 5 (2), 158–164.

Woodland, C., Huang, T.T., Gryz, E., Bendayan, R., Fawcett, J.P., 2008. Expression, activity and regulation of CYP3A in human and rodent brain. Drug Metab. Rev. 40 (1), 149–168. https://doi.org/10.1080/03602530701836712.

Xu, B., Lovre, D., Mauvais-Jarvis, F., 2016. Effect of selective estrogen receptor modulators on metabolic homeostasis. Biochimie 124, 92–97. https://doi.org/10.1016/j.biochi.2015.06.018.

Xu, S.L., Bi, C.W., Choi, R.C., Zhu, K.Y., Miernisha, A., Dong, T.T., Tsim, K.W., 2013. Flavonoids induce the synthesis and secretion of neurotrophic factors in cultured rat astrocytes: a signaling response mediated by estrogen receptor. Evid Based Compl. Alternat. Med. 2013, 127075. https://doi.org/10.1155/2013/127075.

Xu, Y., Nedungadi, T.P., Zhu, L., Sobhani, N., Irani, B.G., Davis, K.E., et al., 2011. Distinct hypothalamic neurons mediate estrogenic effects on energy homeostasis and reproduction. Cell Metab. 14 (4), 453–465. https://doi.org/10.1016/j.cmet.2011.08.009.

Yaffe, K., Krueger, K., Cummings, S.R., Blackwell, T., Henderson, V.W., Sarkar, S., et al., 2005. Effect of raloxifene on prevention of dementia and cognitive impairment in older women: the Multiple Outcomes of Raloxifene Evaluation (MORE) randomized trial. Am. J. Psych. 162 (4), 683–690. https://doi.org/10.1176/appi.ajp.162.4.683.

Yager, J.D., 2015. Mechanisms of estrogen carcinogenesis: the role of E2/E1-quinone metabolites suggests new approaches to preventive intervention–a review. Steroids 99 (Pt A), 56–60. https://doi.org/10.1016/j.steroids.2014.08.006.

Yasuda, Y., Tateishi, N., Shimoda, T., Satoh, S., Ogitani, E., Fujita, S., 2004. Relationship between S100beta and GFAP expression in astrocytes during infarction and glial scar formation after mild transient ischemia. Brain Res. 1021 (1), 20–31. https://doi.org/10.1016/j.brainres.2004.06.015.

Yazgan, Y., Naziroglu, M., 2016. Ovariectomy-induced mitochondrial oxidative stress, apoptosis, and calcium ion influx through TRPA1, TRPM2, and TRPV1 are prevented by 17beta-estradiol, tamoxifen, and raloxifene in the hippocampus and dorsal root ganglion of rats. Mol. Neurobiol. https://doi.org/10.1007/s12035-016-0232-5.

Yu, W., Deng, X., Ma, Z., Wang, Y., 2016. Equol protects PC12 neuronal cells against hypoxia/reoxygenation injury in vitro by reducing reactive oxygen species production. Nan Fang Yi Ke Da Xue Xue Bao 36 (1), 1–7.

Yu, X., Rajala, R.V., McGinnis, J.F., Li, F., Anderson, R.E., Yan, X., et al., 2004. Involvement of insulin/phosphoinositide 3-kinase/Akt signal pathway in 17 beta-estradiol-mediated neuroprotection. J. Biol. Chem. 279 (13), 13086–13094. https://doi.org/10.1074/jbc.M313283200.

Yue, W., Wang, J.P., Li, Y., Fan, P., Liu, G., Zhang, N., et al., 2010. Effects of estrogen on breast cancer development: Role of estrogen receptor independent mechanisms. Int. J. Cancer 127 (8), 1748–1757. https://doi.org/10.1002/ijc.25207.

Yuen, E.C., Mobley, W.C., 1996. Therapeutic potential of neurotrophic factors for neurological disorders. Ann. Neurol. 40 (3), 346–354. https://doi.org/10.1002/ana.410400304.

Zabihi, H., Hosseini, M., Pourganji, M., Oryan, S., Soukhtanloo, M., Niazmand, S., 2014. The effects of tamoxifen on learning, memory and brain tissues oxidative damage in ovariectomized and naive female rats. Adv. Biomed. Res. 3, 219. https://doi.org/10.4103/2277-9175.143297.

Zhang, Y., He, K., Wang, F., Li, X., Liu, D., 2015. Notch-1 signaling regulates astrocytic proliferation and activation after hypoxia exposure. Neurosci. Lett. 603, 12–18. https://doi.org/10.1016/j.neulet.2015.07.009.

Zhang, Y., Jin, Y., Behr, M.J., Feustel, P.J., Morrison, J.P., Kimelberg, H.K., 2005. Behavioral and histological neuroprotection by tamoxifen after reversible focal cerebral ischemia. Exp. Neurol. 196 (1), 41–46. https://doi.org/10.1016/j.expneurol.2005.07.002.

Zhang, Y., Milatovic, D., Aschner, M., Feustel, P.J., Kimelberg, H.K., 2007. Neuroprotection by tamoxifen in focal cerebral ischemia is not mediated by an agonist action at estrogen receptors but is associated with antioxidant activity. Exp. Neurol. 204 (2), 819–827. https://doi.org/10.1016/j.expneurol.2007.01.015.

Zhao, L., O'Neill, K., Diaz Brinton, R., 2005. Selective estrogen receptor modulators (SERMs) for the brain: current status and remaining challenges for developing NeuroSERMs. Brain Res. Brain Res. Rev. 49 (3), 472–493. https://doi.org/10.1016/j.brainresrev.2005.01.009.

Zhou, J.H., Yu, D.V., Cheng, J., Shapiro, D.J., 2007. Delayed and persistent ERK1/2 activation is required for 4-hydroxytamoxifen-induced cell death. Steroids 72 (11–12), 765–777. https://doi.org/10.1016/j.steroids.2007.06.007.

Zhou, W., Koldzic-Zivanovic, N., Clarke, C.H., de Beun, R., Wassermann, K., Bury, P.S., et al., 2002. Selective estrogen receptor modulator effects in the rat brain. Neuroendocrinology 75 (1), 24–33.

Zhou, X., Yang, Z., Han, L., Li, X., Feng, M., Zhang, T., et al., 2015. Raloxifene neutralizes the adverse effects of glutamate on cultured neurons by regulation of calcium oscillations. Mol. Med. Rep. 12 (4), 6207–6214. https://doi.org/10.3892/mmr.2015.4191.

Zou, W., Fang, C., Ji, X., Liang, X., Liu, Y., Han, C., et al., 2015. Estrogen Receptor (ER)-alpha36 is involved in estrogen- and tamoxifen-induced neuroprotective effects in ischemic stroke models. PLoS One 10 (10), e0140660. https://doi.org/10.1371/journal.pone.0140660.