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Chapter 7

ESTROGEN ACTIONS ON GLIAL REACTIVITY AND INFLAMMATION-MEDIATED MEMORY IMPAIRMENT: SEX DIFFERENCES AND INTERACTION WITH OTHER NEUROTROPHIC FACTORS

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ABSTRACT

There is growing evidence that documents profound effects of estrogens on learning, memory, and mood as well as neurodevelopment and neurodegenerative diseases. However, the ability of estradiol to influence synaptic plasticity, neurotransmission, neurodegeneration and cognition, could be different depending on sex dimorphisms. It emerges that estrogens have different, even opposite, effects as well as similar effects in male and female brains. The protective effects of estradiol on neural cells are mediated in part by modulation of neurotrophic factors such as insulin like growth factor (IGF-l), tyrosine kinase A (Trk A), nerve growth factors (NGF), and the like. Also, it modulates the action of neurotrophins, which in turn regulate the synaptogenesis, synaptic plasticity and synaptic functions. By these actions estrogen prevents or slows down the neurodegenerative process. Another described effect of estradiol is the capacity to modulate inflammatory response mediated by glial cells. Neuroinflammation is a feature not only of many neurological disorders but also of aging, and it is accompanied by activation of glial cells and the release of proinflammatory cytokines and chemokines. Such activation is a normal response oriented to protect neural tissue. However, excessive and chronic activation of glia may lead to neurotoxicity and may be harmful for neural tissue. Estrogenic compounds may be candidates to counteract brain inflammation under neurodegenerative conditions by targeting the production and release of pro-inflammatory molecules by glial cells. In this chapter we will review different mechanisms that may be implicated in the diverse actions of estradiol, the differences

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according to gender and we empathize in the anti-inflammatory action on glial cell. We will also explore the interaction of estradiol with others neurotrophic factors, such as IGF-I in the regulation of neurodegeneration and memory impairment. Finally, the possibility of using selective estrogen receptor modulators (SERMs) to exert estradiol-like neuroprotective actions in the brain as an alternative to estrogen will be discussed.

Keywords: estrogen, inflammation, cognition, sex differences, glia

1. INTRODUCTION

Estrogen is a potent steroid of both gonadal and neuronal origin that exerts profound and enduring effects on cognitive function during development, adulthood and aging. Estrogen has traditionally been referred to as the ‘‘female’’ hormone whose principal source is the ovary and consists principally of three forms: 17β-estradiol, estrone, and estriol. However, the male also produces estrogen. In fact, while estrogen levels in the male are quantitatively lower than those in the female, many developmental actions of testosterone in the brain of both sexes depend upon initial intraneuronal conversion by the cytochrome P450 enzyme aromatase to the estrogenic metabolite 17β-estradiol. This steroid subsequently exerts its action on neurons or glia cells by classical or non-classical receptors. Among its various effects estrogen is capable of enhancing synaptic plasticity, neurite growth, hippocampal neurogenesis, and long-term potentiation. It also protects against neuron apoptosis and neural injury in a variety of experimental settings, including toxicity-induced by excitatory neurotransmitters, β-amyloid, oxidative stress, and ischemia (Petrovska et al., 2012). Estrogen can be generated not only from circulating testosterone by local aromatase but synthesized de novo by neurons and glia (Garcia-Segura, 2008).

Many estrogen actions are potentially relevant to cognitive changes occurring after menopause, but for most, the clinical implications are yet unclear (Luine, 2008; Frick, 2009). In theory, estrogen holds great clinical potential for central nervous system (CNS) disorders because of its proven neuroprotective and neuroactivating properties (McEwen & Alves, 1999; Wise et al., 2001; Brann et al., 2007; Garcia-Segura et al., 2008). However, as discussed in detail in the remainder of this chapter, there is mounting evidence that estrogen may have opposite effects in male and female brains which could be due principally to differences in brain organization (for review see Gillies & McArthur, 2010).

2. ESTROGEN AND MEMORY

2.1. General Aspects

Memory comprises acquisition, consolidation and retrieval of information (for review see McGaugh, 2000). Many substances can influence these different phases.

It is well demonstrated that sex hormones, mainly estrogen, impact cognitive function. Estrogen works synergistically with many biologic systems to promote physical, cognitive, and affective function. Basic science reveals that administration of estrogen (estrogen alone and estrogen plus Progesterone) results in increased levels of antioxidants, reduces free

radicals, and substantially lowers oxidative damage to mitochondrial DNA (Irwin et al., 2008). Critical to neuronal health, estrogen also regulates glucose and oxidative metabolism, mitochondrial function, and promotes adenosine triphosphate (ATP) (Brinton, 2008a) Indeed, declines in these processes are characteristic of neurodegenerative diseases such as Alzheimer disease (AD) (Brinton, 2008b). Estrogen treatment promotes the growth of long thin spines in the hippocampus and prefrontal cortex (Wang et al., 2010; Srivastava, 2012; Luine & Frankfurt, 2013), which reduction is correlated with impaired memory function (Luine et al., 2011). Higher levels of presynaptic estrogen receptor α (ERα) are associated with stronger memory performance in ovariectomized animals treated with exogenous estrogen (Wang et al., 2010). Neurotrophins, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), represent another mechanism of neural plasticity in the brain. These substances facilitate the growth of dendritic spines in the hippocampus (Luine et al., 2011). In vitro investigations support a favorable effect of estrogens on the activity of neurotropins (Green et al., 2000; Solum & Handa, 2002). By rising hippocampal BDNF levels, estrogen transiently increases dendritic spines, thereby potentiating opportunity for increased connectivity and plasticity (Srivastava, 2012).

Estrogen also interacts with a number of neurotransmitters affecting cognition and mood. Animal research reveals that long-term use of estrogen prevented declines in cholinergic nerve cell fiber length and density at menopause (Tinkler et al., 2004). In humans, the negative effect of cholinergic challenge on cognitive performance and neural activation patterns was counteracted by prior exposure to estradiol (Dumas et al., 2006; 2012). Of note, naturally occurring higher levels of estriol were associated with poorer cognition, specifically working memory performance (Dumas et al., 2012).

2.2. Sex Differences

Many estrogen effects differ qualitatively or quantitatively between the sexes, suggesting that they may be subject to sexual differentiation during pre- or early postnatal development. In addition, circulating hormone levels may contribute differentially in adult males and females.

It is well documented that men and women have different types of cognitive function, and the sex differences in cognition are associated with brain estrogen and testosterone actions in the regions important for cognition, memory and mood such as the cortex, hippocampus and amygdala (Wilson & Davies,1973; Cahill, 2006; Cosgrove et al., 2007).

Gender differences in cognitive function have been well demonstrated in adulthood as well as ageing. For example, men demonstrated larger amygdala and thalamus volumes compared to women (Neufang et al., 2009; Bramen et al., 2011; Koolschijn & Crone, 2013), whereas the size of the hippocampus is larger in females compared to males (Neufang et al., 2009; Giedd et al., 1996). It is also worth noticing that there are a relatively higher number of androgen receptors in the amygdala (Clark et al., 1988) and a relatively higher number of estrogen receptors in the hippocampus (Morse et al., 1986). The sex differences in regional brain structure might be responsible for the sex differences in specific cognitive and behavioral tasks (De Vries, 2004; Cahill, 2006; Cosgrove et al., 2007).

Sex differences in brain function also include gender differences in the incidence of psychopathologies such as depressive illness, which is more common in women; substance

abuse and antisocial behavior, which are more common in men, as well as pain sensitivity. The diversity of these effects implies that regions of the brain are involved outside of the hypothalamus, which has been the traditional site for the study of ovarian steroid receptors and their role in the control of reproductive function. The actions of estrogen could be mediated by intracellular receptors, which modulate genomic actions, or by membrane receptors or indirectly by their actions on glial cells (the mechanisms of action will be discuss in another section of this chapter).

Due to the hippocampus is one of the major areas related to memory process, this section emphasizes in the sex differences and estradiol actions concerning to this region even so it will also be discuss the differences in the prefrontal cortex (PFC), another brain area involved in memory.

In experimental mammalian species, such as rats, and in humans, males perform better than females, on average, in the acquisition of tasks involving spatial memory, which are highly dependent on the hippocampus (Luine, 2008; Mitsushima et al., 2009). The activation influences of adult gonadal steroids play an important role in maintaining sexually differentiated cognitive behaviors.

Many studies investigating only females report a positive effect of estrogens on hippocampal- dependent tasks in rats, mice, and rhesus monkeys (Foster et al., 2008; Luine, 2008; Spencer et al., 2008). Relatively few studies have made direct comparisons of males and females, but in some tests of hippocampal spatial discrimination (the Morris water maze), hormone treatment of gonadectomized mice revealed that estradiol selectively impaired performance in females but had no effect in males (Fugger et al., 1998). Several reports suggest that functional sex differences are related to organizational influences in early development (Roof, 1993; McEwen & Alves, 1999; Romeo et al., 2004).

For example, exposure to high levels of estradiol during development improves (masculinizes) spatial behavior in adult female rats to levels seen in normal males. It seems therefore that sex differences in aspects of hippocampal function are determined by testosterone acting after conversion to estrogen by aromatase in a manner similar to that established for the hypothalamus, indicating that non-reproductive brain regions are subject to hormonal processes of sex differentiation similar to those in brain regions intimately associated with reproduction.

It should be noted, however, that in other tests of hippocampal function (a delayed matching-to-position task), estradiol treatment of rats gonadectomized as adults enhanced task acquisition in both sexes and, although testosterone treatment of males was without effect on this component of the task, testosterone did affect delay-dependent working memory (Gibbs, 2005).

Furthermore, both human and animal studies showed that administration of androgens to females may induce male-typical cognition and behavior, and the male-type cognition disappearing when the treatment was withdrawn (Cahill, 2006). For example, one recent cross-sectional human study showed that women with polycystic ovary syndrome characterized by elevated endogenous testosterone performed significantly better at three-dimensional mental rotation, a male favored cognitive behavior, than a female control group (Barry et al., 2013).

Another study also demonstrated that a single administration of testosterone improves 3D mental rotation abilities in young women (Aleman et al., 2004).

On balance, it seems that estrogens and androgens influence different aspects of cognitive tasks or domains in males and females, with indications that these effects are sex-specific (Warren & Juraska, 1997; Gibbs, 2005).

Indeed, it is generally thought that males and females use different strategies, underpinned by different organization of the underlying neural substrate, to solve similar spatial tasks; females tend to rely more on local cues and landmarks, whereas males rely more on the spatial relationships between two fixed points (Raber, 2008). The available evidence also suggests that hormonal influences can differ with the type of task, the aspect of the task under investigation (acquisition, consolidation, retrieval), and the degree to which the task relies on input from brain regions other than the hippocampus, such as the prefrontal cortex, which is associated more with working memory tasks requiring visual object information (Torres-Aleman et al., 1990; Takase et al., 2009).

Concerning the prefrontal cortex, it plays an important role in working or short-term memory in various mammalian species, including rats, nonhuman primates, and humans. Tests of prefrontal functions reveal many sex differences: females generally outperform males in the acquisition of tasks that rely more heavily on this region, such as visual object recognition (Kritzer et al., 2007; Luine, 2007; Mitsushima et al., 2009). Although the organizational and activational influences of sex hormones have not be studied as extensively in this region as the hippocampus, emerging evidence suggests the impact of both estrogens and androgens in both sexes (Gibbs, 2005). For example, estradiol promotes performance in memory tasks in women (Berman et al., 1997; Keenan et al., 2001), female rhesus monkeys (Wang et al., 2010), and rats (Wallace et al., 2006), and circulating levels of both estradiol and testosterone correlate with certain spatial and mnemonic tasks in female rats (Kritzer et al., 2007). In adult male rats, gonadectomy impairs performance in various tasks of working memory and other types of cognitive tasks that are known to rely on the PFC, but the hormone responsiveness depends on the task and probably the neurotransmitter pathways involved.

Hence, testosterone, but not estradiol, reversed the effects of castration on performance in tests of spatial working memory, and this correlated with the density of dopaminergic terminals in the medial PFC. Like the hippocampus, the PFC retains the capacity for synaptic remodeling, which is also critical for learning and memory that is lost in AD (Scheff & Price, 2003).

Estradiol also maintains dendritic spines in specific cortical regions of female nonhuman primates (Tang et al., 2004) and rats (Wallace et al., 2006), in parallel with positive effects on working memory; preliminary studies indicate that androgens may also positively affect spine synapses in the female PFC (Hajszan et al., 2008).

Although work in this brain region is still at an early stage, both morphological and behavioral studies suggests that the PFC uses sex hormones in a manner different from that seen in the hippocampus and hypothalamus, suggesting that hormonal therapeutic strategies to modulate the function of each of these brain regions could be achieved by a different cocktail of hormone supplementation that might be unique to males or females.

Therefore, at behavioral level it is very difficult to reach simple interpretations on the influences of estradiol or testosterone on cognition in males and females. In contrast, striking sexually dimorphic responses to estradiol have been reported for neuroanatomical, morphological, neurochemical, and electrophysiological correlates of learning and memory.

3. MECHANISMS OF ACTION

3.1. Nuclear and Extra-Nuclear Mechanisms for Genomic and Rapid, Non-Genomic Mechanisms of Estrogen Signaling in the Brain

The last decade or so has seen very rapid advances in our understanding of the mechanisms of action of estrogen in the brain, as evidenced by many excellent reviews (McEwen & Alves 1999; Toran-Allerand et al., 1999; Wise et al., 2001; Brann et al., 2007; Tetel, 2009; Arevalo et al., 2015). Here there are summarizing some basic background information on cellular signaling mechanisms and ER expression patterns:

1. Classic Estrogen Receptors. Classic ERs are located in the nucleus and cytoplasm of the cell and belong to the nuclear receptor superfamily, members of which act as nuclear ligand-gated transcription factors, binding to estrogen response elements (EREs) within specific genes to alter their rate of transcription (Mangelsdorf et al., 1995). The two known isoforms, ERa and ERb are coded by separate genes and are located throughout the brain, but have a differential distribution. ERα mRNA is widely distributed in many brain regions, including the hippocampus, hypothalamus, amygdala, and brainstem nuclei, and co-localizes with ERβ mRNA in many regions. ERβ has a more restricted distribution and is found in particular abundance in human, nonhuman primate, and rodent hippocampus and selected hypothalamic nuclei, especially the supraoptic and paraventricular nuclei (PVN) (Shughrue et al., 1997, 1998; Register et al., 1998; Gundlah et al., 2000; Osterlund et al., 2000a,b; Mitra et al., 2003; Ostlund et al., 2003; Merchenthaler et al., 2004; Suzuki and Handa, 2005; Gonzalez et al., 2007; Weiser et al., 2008). The two forms of ER are structurally and functionally distinct, each regulating unique sets of target genes in a tissue- and cell type-specific manner (Kian Tee et al., 2004). This may be the net effect of homo- or hetero-dimerization of ERα and ERβ. Steroid receptor-mediated transcription is also modulated by corregulators (activator and repressor proteins and protein complexes). There are vast numbers of these corregulator proteins, and various selective combinations associate with ERs and critically determine the region and cell-type specificity of the effects of ER ligands, as well as potential interactions of ER with other nuclear receptors, such as those for progesterone (PR), testosterone, androgen receptors (AR), and glucocorticoids (Tetel, 2009). As well as acting directly through EREs, ligand-activated classic ERs can also modulate gene transcription indirectly at alternative response elements by influencing the activity of other transcription factors. Specifically, estradiol can activate transcription via the activated protein-1 response element in the presence of ERα but fails to do so when linked with ERβ (Kushner et al., 2000). The expression, co-expression, and ratio of ERα / ERβ, as well as the presence of any given combination of co-regulatory proteins in any given cell, will therefore greatly influence the estrogen response.

2. Membrane Signaling. In addition to classic genomic actions, it is now recognized that estrogens can initiate rapid signaling via actions at the cell membrane in many brain regions. Because there is no clear consensus on the molecular identity of the membrane receptors, it is not possible to define their expression patterns in the brain. However, pharmacological and emerging ultrastructural evidence demonstrates that classic "nuclear" ERα and ERβ, and probably other novel receptors (such as GPR30), can also be localized at the cell membrane to effect rapid activation of intracellular brain signaling pathways and modulatory proteins

within seconds to minutes of exposure to steroid (McEwen & Alves, 1999; Gorosito et al., 2008; Vasudevan & Pfaff, 2008; Mermelstein, 2009) These include effects on calcium channels and intracellular stores to increase intracellular [Ca2], which may lead to activation of calcium-calmodulin-dependent kinases, and activation of other protein kinases in 1) the cAMP/cAMP-dependent protein kinase pathway, 2) the mitogen-activated protein kinase (MAPK or extracellular signal-regulated kinases, ERK) pathway (also named MEK), and 3) the phosphoinositide 3-kinase (PI3K)/Akt (also termed PKB) pathway. In parallel or in series, these pathways may interact and converge, finally to affect gene transcription and protein synthesis via the rapid downstream activation of transcription factors, such as the cAMP response element binding protein (CREB) or nuclear factor κB (Toran-Allerand et al., 1999, 2002; Boulware et al., 2005; Vasudevan & Pfaff, 2008; Mermelstein, 2009). Thus, although referred to as non-genomic mechanisms to distinguish them from the classic mode of action, it is now understood that actions initiated at the plasma membrane may also ultimately affect gene transcription. The mechanisms by which activated membrane ERs elicit cellular responses are not yet understood, but interactions with other cell-surface receptors and their associated molecules, such as G-proteins, insulin-like growth factor 1 (IGF-I), and metabotropic glutamate receptors (which are linked to G-proteins) have emerged as means by which membrane ERs can trigger intracellular second- messenger signaling systems and affect cellular responses (Garcia-Segura et al., 2001; Wyckoff et al., 2001; Mermelstein, 2009). Estrogen-activated signaling pathways can also increase mitochondrial efficiency and lead to a reduction in free radical generation in the brain and mitochondrial-dependent apoptosis (Nilsen et al., 2007; Brinton, 2008a). Furthermore, membrane- initiated and genomic actions of hormones may be coupled, so the distinctions are not as clear-cut as was first thought (Vasudevan & Pfaff, 2008). It is noteworthy that most of the cellular mechanisms described for estrogen actions, especially MEK/ERK and PI3K/Akt signaling and mitochondrial function, have important roles in cell survival, apoptosis, function, and neurodevelopment and may sub-serve the critical neuroregulatory, neurotrophic, and neuroprotective effects of estrogens in brain physiology and pathological conditions of the brain. There is, however, no simple rule to predict which mode of estrogenic action will prevail and whether estrogens will exert positive/enhancing or negative/ suppressing influences on any given signaling pathway because, notoriously, these vary between neural phenotype and brain region.

3.2. Interaction with Other Neurotrophic Factors

Estradiol exerts its actions via different mechanisms, one of which involves interacting with different neurotrophic factor receptors. Among them is IGF-I, that is a potent neuroprotective hormone (Torres Aleman, 2012). There is a substantial body of evidence of a close interdependence between the actions of IGF-I and estradiol in the brain (Mendez et al., 2005). Both factors have in common the duality of being hormones, as well as locally produced neuromodulators, and they exert similar pleiotropic actions in the developing and adult brain. There are several potential points of convergence between estradiol and IGF-I receptor (IGF-IR) signaling in the brain. Estrogen activates the mitogen-activated protein kinase (MAPK) pathway and has a synergistic effect with IGF-I on the activation of Akt, a kinase downstream phosphoinositol-3 kinase. In addition, IGF-IR is necessary for the

estradiol induced expression of the anti-apoptotic molecule Bcl-2 in hypothalamic neurons. The interplay of ERs and IGF-IR in the brain may depend on interactions between neural cells expressing ERs with neural cells expressing IGF-IR, or on direct interactions of the signaling pathways of ERs and IGF-IR in the same cell, since most neurons expressing IGF-IR also express at least one of the ER subtypes (Cardona-Gómez et al., 2001; Cardona-Gómez et al., 2002; Garcia-Segura et al., 2010). It is also known that IGF-I regulates ER transcriptional activity and, as we mentioned above, estradiol regulates IGF-I receptor signaling in neural cells and some details on the molecular mechanisms involved in this cross-talk have been established. IGF-I is required to maintain a broad range of brain functions (Carro et al., 2003) regarding modulation of cognition, IGF-I is associated with increases in speed of information processing and working memory (Aleman et al., 1999; Bellar et al., 2011). Future directions may include the assessment of the interaction of ERs and IGF-I receptors with other signaling systems.

Another neurotrophic factor of relevance is BDNF. It was shown that estrogen can induce BDNF expression via an estrogen-sensitive response element on the BDNF gene. It was subsequently shown that BDNF mRNA levels increase in many brain areas of ovariectomized rats treated with estradiol (Singh et al., 1995; Sohrabji et al., 1995; Solum & Handa, 2002). BDNF is a member of the neurotrophin family, which includes nerve growth factor, neurotrophin-3, and neurotrophin-4/5. All neurotrophins have potent actions at tropomyosin receptor kinases (trk). BDNF binds with high specificity to trkB. It is well documented that BDNF potentiates synaptic transmission in hippocampal area CA1, area CA3, and the dentate gyrus, and is critical to the late phase of long-term potentiation (Patterson et al., 1996; Pang and Lu, 2004). In area CA3, BDNF potentiates a major glutamatergic input to pyramidal cells, the mossy fiber pathway (Scharfman, 1997). These studies suggested that BDNF might be a mediator of estrogen action.

4. Inflammation and Cognitive Impairment

4.1. Overviews

The neural cell response to injury is known as neuroinflammation. Two types of inflammatory responses are known to occur in the CNS, acute and chronic. Acute inflammation comprises a rapid activation of glial cells: microglia and astrocytes and the release of a set of growth factors and proinflammatory molecules in the surrounding and within the damaged tissue. These factors restore the stability and function of adjacent nervous cells in a paracrine way; it is basically a defensive response directed to repair the damaged site. Nevertheless as time progresses, chronic proinflammatory cytokines and chemokines attract macrophages/microglia and T cells to the focus of inflammation that promote further injury and propagate a feed-forward inflammatory response resulting in a progressive neurodegeneration and cognitive decline. Neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases and stroke are often accompanied by chronic inflammatory events (Hensley, 2010; Baune, 2015).

Also, it has been described that pro-inflammatory markers increase with age, and correlate with deleterious cognitive outcomes in late life (Franceschi et al., 2000; Kravitz et

al., 2009; Bettcher et al., 2012). In terms of underlying mechanisms, older adults with higher systemic levels of inflammatory markers have been shown to evidence smaller hippocampi and medial temporal lobes relative to those with low levels of inflammation (Bettcher et al., 2012). Although much of the injury caused by chronic inflammation is irreversible, the progressive nature of this reaction allows interferences at delayed time points when anti-inflammatory agents can inhibit glial cell activation and release of proinflammatory cytokines.

4.2. Estrogen and Inflammation

The neuroprotective and anti-inflammatory effects of estradiol in the brain are mediated, at least in part, by a reduction of reactive gliosis (Arevalo et al., 2010). Estradiol exerts anti-inflammatory effects on astrocytes and microglia by mechanisms involving estrogen receptors (Arevalo et al., 2010). For instance, estrogens decrease the expression of nitric oxide and the inflammatory markers TNFa, IL-1b, IL-6, matrix metalloproteinase- 9, and interferon-inducible protein-10 in cultured astrocytes incubated with bacterial LPS (Kipp et al., 2007; Lewis et al., 2008; Cerciat et al., 2010) by mechanisms that involve the inhibition of NFκB-induced transcription of proinflammatory chemokines and cytokines (Dodel et al., 1999; Cerciat et al., 2010). Furthermore, estrogens decrease the number of reactive astrocytes in vivo, after excitotoxic-induced neurodegeneration (Ciriza et al., 2004), in experimental Parkinson's disease (Tripanichkul et al., 2006), in experimental diabetic central neuropathy (Saravia et al., 2006), after lesion of the cholinergic basal forebrain (Martinez & de Lacalle, 2007), and after stab wound brain lesions (García-Estrada et al., 1999; Barreto et al., 2007; Barreto et al., 2009).

4.3. Glial Cells Mediate Hormonal Signaling

It is becoming increasingly apparent that glial cells of the central and peripheral nervous system are key participants because they are capable of both sending and receiving hormonal signals. Hormones are also a critical component of neuronal/glial cross talk, leading to neuromodulatory and neurotrophic actions under physiological and pathological conditions (Garcia-Ovejero et al., 2005).

Both Schwann cells, in the peripheral nervous system, and oligodendroglia, astroglia, NG2 cells and microglia, in CNS, are targets of the hormone. Glial cells are involved in a large variety of functions, including the regulation of neuronal metabolism, neuronal activity and synaptic transmission and plasticity. In addition, Schwann cells and oligodendrocytes produce myelin, which is essential for the quick propagation of impulses in axons (Volterra et al., 2002).

Glial cells express classical ERs (Garcia-Ovejero et al., 2005) and this expression is enhanced under different pathological conditions (Blurton-Jones & Tuszynski, 2001; Savaskan et al., 2001; García-Ovejero et al., 2002; Takahashi et al., 2004); this may facilitate actions of estradiol to reduce neuronal damage (Carbonaro et al., 2009). Estradiol also exerts rapid signaling events in glia via membrane-associated ERs (Grove-Strawser et al., 2010), the regulation of the activation of kinase signaling pathways (Ivanova et al., 2001; Zhang et al.,

2002; Dhandapani et al., 2005; Hirahara et al., 2009), and the modification of intracellular calcium levels (Chaban et al., 2004; Arnold, 2005). Furthermore, ER independent antioxidant actions of estradiol may reduce oxidative stress mechanisms involved in glial activation (Wang et al., 2006). The reaction of glial cells to neurodegenerative damage is a complex phenomenon that includes a mixture of positive and negative responses for neuronal survival and regeneration.

After peripheral nerve injury Schwann cells proliferate, form a permissive environment for axonal growth and re-myelinate the growing axons (Fawcett & Keynes, 1990; Chen et al., 2007). In the injured CNS oligodendrocyte precursor cells are activated to generate re-myelinating oligodendrocytes, which restore myelin in demyelinated damaged axons (Franklin et al., 2008). Astrocytes become reactive, increasing their volume and the expression of intermediate filaments such as glial fibrillary acidic protein (GFAP), vimentin and nestin. Reactive astrocytes maintain the integrity of the blood–brain barrier and the survival of peri-lesion tissue by the release of molecules, including estradiol (Garcia-Segura et al., 2003; Saldanha et al., 2009), that exert neuroprotective actions on neurons. However, reactive astrocytes interfere with axonal regeneration and contribute to local brain inflammation (Laird et al., 2008). Reactive microglia exerts important positive functions by remodeling the damaged tissue, but release proinflammatory cytokines and may exacerbate neuronal damage (Hanisch & Kettenmann, 2007).

Anti-inflammatory effects of estradiol on astrocytes may also contribute to the neuroprotective effects of the hormone. Under pathological conditions, astrocytes release a number of proinflammatory cytokines and chemokines that attract macrophages/microglia and T cells to CNS inflammatory sites.

The downregulation of the production of cytokines and chemokines by reactive astrocytes may be involved in the neuroprotective mechanisms of estradiol, at least under chronic neurodegenerative conditions. The anti-inflammatory effects of estradiol may involve ERs expressed in astrocytes. A study using selective ERα and ERβ specific ligands suggests that both receptor subtypes are involved in the anti-inflammatory action of estradiol on astrocytes in vitro (Lewis et al., 2008).

Estradiol also reduces CNS inflammation acting on microglia. Activation of microglia is a normal response from neural tissue to cope with infections and neurodegeneration and it is oriented to protect neural tissue. However, exaggerated and chronic activation of microglia may lead to neurotoxicity and may be detrimental for neural tissue (Streit, 2002; Block et al., 2007; Lehnardt, 2010; Baune, 2015). Therefore, the regulation of the response of microglial cells to inflammation may represent a therapeutic approach to control neurodegeneration. Studies in microglia cultures have shown that estradiol inhibits the induction of inducible nitric oxide synthase and several other inflammatory mediators in response to LPS and to proinflammatory cytokines (Bruce-Keller et al., 2000; Drew & Chavis, 2000; Dimayuga et al., 2005; Vegeto et al., 2008). Studies in vivo have also demonstrated that estradiol reduces microglia reactivity and the expression of cytokines and chemokines induced by an acute intracerebroventricular injection of LPS in female mice (Vegeto et al., 2003; Vegeto et al., 2006; Vegeto et al., 2008) and by the systemic administration of LPS (Tapia-Gonzalez et al., 2008). The hormone also reduces microglia activation after a stab wound injury.

Recent studies have investigated the actions of estradiol on oligodendrocytes and myelin integrity after different forms of white matter injury. The results have shown that estradiol is able to reduce, at least partially, oligodendrocyte cell loss and demyelination and to facilitate

remyelination (Crawford et al., 2010). The protective actions of estradiol on oligodendrocytes and myelin may be mediated by the hormonal control of peripheral immune cells (Du et al., 2011) and by direct actions on oligodendrocytes (Hirahara et al., 2009).

Therefore the actions of estradiol on glial cells are important to maintain physiological homeostasis, control the inflammation and ameliorate the cognitive impairment observed with aging or under pathological conditions.

5. Potential for Estradiol or Brain-Selective Estrogen Receptor Modulators-Therapies

As it has already discussed, there are numerous neuroprotective actions of estrogens that have direct relevance to neurodegenerative diseases and inflammation-associated decline in cognition. Despite these actions, the promise of estrogen-based therapies for reducing the risk for neurodegeneration remains to be fulfilled. The application of estradiol as a neuroprotectant in humans presents numerous limitations, mainly due to the endocrine actions of the molecule on peripheral tissues, including estrogen dependent tumors. Therefore, as ongoing research continues to address these crucial and immediate concerns, an emerging area of investigation is the development of natural and synthetic hormone mimetics that will preferentially activate estrogen neuroprotective mechanisms while minimizing adverse effects in other tissues.

The possibility of using selective estrogen receptor modulators (SERMs) to exert estradiol-like neuroprotective actions in the brain has emerged as an alternative to estradiol (DonCarlos et al., 2009). According to chemical family, SERMs are classified as first-generation SERMs, such as tamoxifen and its derivatives, second-generation SERMs, such as raloxifene, and third-generation SERMs. Fourth-generation SERMs are benzopyran compounds (Dowers et al., 2006). SERMs bind to estrogen receptors (ERs) and induce specific changes in their three-dimensional conformation (Brzozowski et al., 1997; Paige et al., 1999) allowing a tissue-selective recruitment of transcriptional cofactors (Klinge, 2000; McKenna & O'Malley, 2002; Belandia & Parker, 2003). Therefore, SERMs may act as ER agonists in the brain and as antagonists in others tissues, such as breast tumors.

The neuroprotective actions of tamoxifen and raloxifene, have been assessed in different experimental models of neural dysfunction. These include animal models of traumatic injury of the central nervous system and peripheral nerves, stroke, multiple sclerosis, Parkinson's disease, Alzheimer's disease, cognitive decline, and mood disorders.

In general, there is still poor knowledge of the precise molecular targets of SERMs in the nervous system. Although some key molecules have been identified, such as MAPK, PI3K/Akt, CREB, and NF-kB, the molecular mechanisms involved in the neuroprotective actions of SERMs should be investigated with more detail in the different cellular populations of the nervous system. Ideally, SERMs with cellular specificity for neurons, astrocytes, oligodendrocytes, and microglia may promote cell-specific responses to decrease neuronal death, increase re-myelination, enhance the production of neuroprotective growth factors by astrocytes, and reduce the chronic proinflammatory response of astrocytes and microglia.

There are considerable precedents to fuel efforts to develop SERMs with selectivity for the brain, and not peripheral targets, which could eliminate unwanted peripheral actions of

estrogens, including their feminizing actions, thereby making them accessible for men as well as women.

CONCLUSION

The studies reviewed here clearly support that estrogens exert their neuroprotective effects in part by regulating the brain inflammation under physiological conditions, like aging; or neurodegenerative diseases, like Alzheimer or Parkinson. These actions are mediated, in part, by glia cells.

The ability of estradiol to influence cognitive impairment associated with aging or neurodegenerative diseases, depends on the sex or the brain area under study.

However, there are many aspects that still need to be addressed, including determination of the best estrogenic formulations and whether cyclic versus continuous hormone therapy delivery is most suitable for promoting brain function and cognition. In addition, it is important to understand the role that other factors, such as IGF-I and the different cellular and subcellular targets of estradiol, play in the neuroprotective mechanisms of the hormone. Another important consideration is that although estradiol is neuroprotective, its peripheral actions limit its use for the treatment or prevention of neurodegenerative diseases and affective disorders. Therefore, new alternatives to estradiol therapy based on the neuroprotective mechanisms of the hormone are being explored. SERM's, may represent an alternative to estradiol and may also be used in males.

Further developments may include the use of aromatase modulators to selectively increase brain estradiol synthesis as an alternative to the administration of estrogenic compounds. Given the importance of the interactions of estradiol and IGF-I neuroprotective mechanisms, the outcome of the modulation of IGF-I levels in parallel with administration of estrogenic therapies should also be explored in experimental neurodegenerative models.

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