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Review

Estrogen receptor agonists for attenuation of neuroinflammation and neurodegeneration

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ABSTRACT

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

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1. Introduction

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

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

The innate immune responses are regulated by the complex signaling pathways between the immune system and the CNS in the brain (Rivest, 2009). Microglia are involved in activation of astrocytes and migration of peripheral immune cells (Voskuhl et al., 2009; Sofroniew and Vinters, 2010) to respond to infection or injury in the brain. Estrogens and ER agonists could modulate the activation of many different cell types of the immune system (Straub, 2007) and the CNS (Spencer et al., 2008; Dumitriu et al., 2010). Recent investigation suggests that estrogens can suppress the activation of microglia and recruit the blood-derived monocytes in rat brain after intracerebroventricular injection of bacterial lipopolysaccharide (LPS) (Vegeto et al., 2003). This investigation also showed an increase in expression of C3 receptor and matrix metalloproteinase-9 (MMP-9) following LPS exposure (Vegeto et al., 2003). Estrogens can also inhibit expression of pro-inflammatory cytokines such as IL-1β and TNF-α in primary astrocytes following LPS exposure (Lewis et al., 2008). These studies suggest that depending on the signaling mechanisms, estrogens can play dual roles for attenuation of neuroinflammation and neurodegeneration by inhibiting activation of microglia and astrocytes (Fig. 1).

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

2. Estrogen receptors (ERs) and their subtypes

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

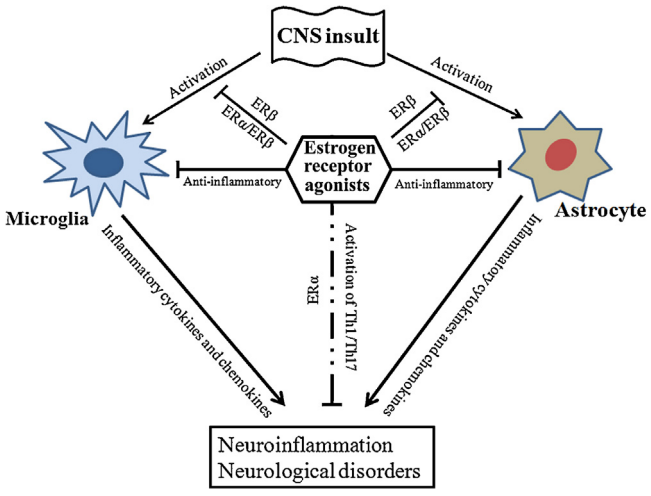

Fig. 1. A schematic presentation of anti-inflammatory roles of estrogen and ER agonists in neurodisorders. Insults to the CNS lead to overactivation of microglia and astrocytes. Activated microglia and astrocytes can release pro-inflammatory cytokines and chemokines to induce neuroinflammation to promote pathogenesis in different neurodisorders. Treatment with ER agonists can be useful to inhibit the activation of microglia and astrocytes after the CNS insults. Estrogen driven Th1/Th17 cell response is thought to be carried out via involvement of ERα.

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