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Review

Role of astrocytes in the neuroprotective actions of 17β-estradiol and selective estrogen receptor modulators

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ABSTRACT

Neuroprotective actions of 17β-estradiol (estradiol) are in part mediated by direct actions on neurons. Astrocytes, which play an essential role in the maintenance of the homeostasis of neural tissue, express estrogen receptors and are also involved in the neuroprotective actions of estradiol in the brain. Estradiol controls gliosis and regulates neuroinflammation, edema and glutamate transport acting on astrocytes. In addition, the hormone regulates the release of neurotrophic factors and other neuroprotective molecules by astrocytes. In addition, reactive astrocytes are a local source of neuroprotective estradiol for the injured brain. Since estradiol therapy is not free from peripheral risks, alternatives for the hormone have been explored. Some selective estrogen receptor modulators (SERMs), which are already in use in clinical practice for the treatment of breast cancer, osteoporosis or menopausal symptoms, exert similar actions to estradiol on astrocytes. Therefore, SERMs represent therapeutic alternatives to estradiol for the activation of astroglia-mediated neuroprotective mechanisms.

Contents

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ApoE, apolipoprotein E; BDNF, brain derived neurotrophic factor; CREB, cAMP response element-binding protein; DMT, dimethoate; DPN, diarylpropionitrile (2,3-*bis*(4-Hydroxyphenyl)-propionitrile estrogen receptor β agonist); EAE, experimental autoimmune encephalomielytis; ER, estrogen receptor; Gαq-mER, Gαq-coupled membrane-associated estrogen receptor; GDNF, glial cell derived neurotrophic factor; GFAP, glial fibrillary acidic protein; GLAST, glutamate aspartate transporter; GLT, glial glutamate transporter; GPER, G protein-coupled estrogen receptor 1; IGF1, insulin-like growth factor-1; IL, interleukin; IP10, interferon-γ-inducible protein 10; LPS, lipopolysaccharide; MMP-9, matrix metalloproteinase-9; Ngb, Neuroglobin; NFκB, nuclear factor κB; NGF, nerve growth factor; PI3K, phosphatidylinositol 3-kinases; PPT, 4,4′,4″-(4-Propyl-[1H]-pyrazole-1,3,5-triyl) trisphenol (estrogen receptor α agonist); SERMs, selective estrogen receptor modulators; Src, sarcoma; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

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1. Introduction

Neuroprotective actions of 17β-estradiol (estradiol) have been extensively studied in different experimental models of neurodegenerative diseases (Azcoitia et al., 2011a; Scott et al., 2012). The mechanisms involved in these protective effects have also been explored and include (i), nuclear-initiated estrogen receptor (ER) signaling by the direct or indirect regulation of transcriptional activity by ERs α and β; (ii), membrane-initiated ER signaling by actions on membrane associated ERα, ERβ, Gαq-coupled membrane-associated ER (Gαq-mER) and G protein-coupled ER 1 (GPER); (iii), the regulation of different signaling pathways, such as the phosphatidylinositol 3-kinases (PI3K) kinase, extracellular signal-related kinase pathways, sarcoma (Src) family kinases and cAMP/protein kinase A, among others, and (iv), the interaction with other signaling molecules that regulate neuronal survival, such as Wnt, insulin-like growth factor-1 (IGF1), glial cell derived neurotrophic factor (GDNF) and brain derived neurotrophic factor (BDNF) (Qiu et al., 2006; Zhang et al., 2008; Garcia-Segura et al., 2010; Liu et al., 2012; Schreihofer and Ma, 2013; Scott and Brann, 2013). Estradiol directly activates these protective mechanisms on neuronal populations expressing estrogen receptors. Indeed, in vitro studies have demonstrated that estradiol exert direct protective actions on neurons, in absence of glial cells. Furthermore, the implication of neurons in the neuroprotective actions of estradiol in vivo has been demonstrated in a model of experimental stroke using neuron-specific ERα deletion (Elzer et al., 2010). However, it is important to consider that in the nervous system there is a crosstalk between its different cellular populations and, therefore, other cell types, including astrocytes, microglia, oligodendrocytes and endothelial cells, are involved in the protective and reparative actions of the hormone in vivo (Garcia-Ovejero et al., 2005).

In this review we will focus on the role of astrocytes on the protective actions of estradiol on the central nervous system and we will discuss the mechanisms involved in the contribution of astrocytes to estradiol-induced neuroprotection. In addition, we will also review the role of astrocytes on the neuroprotective actions of selective estrogen receptor modulators (SERMs), since these molecules are potential therapeutic candidates for the treatment of neural diseases (Arevalo et al., 2011).

2. Astrocytes are cellular targets of estradiol

2.1. Estradiol regulates astrocyte morphology and function

For many years it was considered that neurons were the main cellular target for the action of estradiol in the nervous system. Thus, numerous studies examined the action of the hormone on the development and plasticity of different neuronal populations in different brain regions. However, from the early autoradiographic studies by Pfaff and colleagues to identify the cell types that accumulated radioactive estradiol in the brain (Pfaff and Keiner, 1973; Pfaff et al., 1976) it was evident that hormone receptors were present not only in neurons but also in other cell types. Later on, electron microscope studies conducted in the hypothalamus to determine whether estradiol regulated synaptic plasticity, revealed that the hormone promotes the growth of astrocyte processes (see Garcia-Segura et al., 1994a,b for references). The action of estradiol on the growth of astrocyte processes was confirmed using immunohistochemistry for glial fibrillary acidic protein (GFAP), was also detected in other brain regions, such as the hippocampus (Tranque et al., 1987; Garcia-Segura et al., 1989; Luquin et al., 1993) and was shown to be accompanied with an increase in GFAP expression (Kohama et al., 1995; Stone et al., 1998). More recent studies have shown that estradiol regulates different functional parameters in astrocytes, such as intracellular Ca^{++} levels (Chaban et al., 2004; Arnold, 2005; Micevych et al., 2010), which in turn may influence the communication of astrocytes with neurons and with other glial cells (Perea and Araque, 2010). Estradiol also regulates the expression of a variety of proteins in astrocytes that participate in the regulation of neuroinflammation, extracellular glutamate levels and neuronal homeostasis (see Garcia-Segura and Melcangi, 2006, for review and Section 4). Some of these actions of estradiol on astrocytes are involved in the neuroprotective effects of the hormone (Fig. 1 and Table 1).

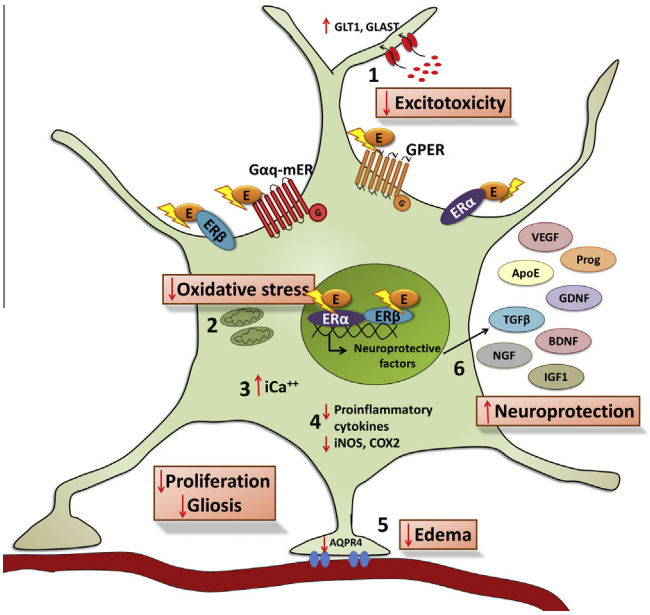

Fig. 1. Summary of the actions elicited by estradiol (E) in astrocytes that may be involved in neuroprotection. These actions include: (1) increase in the expression of glutamate transporters (GLT1, GLAST), with the consequent decrease of extracellular glutamate concentrations and reduction of excitotoxicity; (2) protection of the mitochondrial function and decrease of oxidative stress and oxidative cell death, allowing, therefore, the glial release of trophic factors for neurons; (3) increase in intracellular Ca^{++} levels, which may affect glia to glia and glia to neuron communication; (4) reduction in the activation of the mechanisms of gliosis and reactive astroglia proliferation and reduction in the expression of proinflammatory molecules (cytokines, chemokines, iNOS, COX2), with the consequent regulation of the neuroinflammatory response of the damaged tissue; (5) regulation of the expression of aquaporin 4 (AQPR4), with the consequent control of edema and (6) increase in the expression and release of neuroprotective factors, such as VEGF, progesterone (Prog), ApoE, GDNF, TGFβ, BDNF, NGF, IGF1, with the consequent promotion of neuronal survival. These actions are mediated by nuclear initiated signaling through ERα and ERβ regulated transcription and by membrane initiated signaling through ERα and ERβ associated to the membrane and by membrane ERs (Gαq-mER and GPER).