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Review

Astrocyte-derived growth factors and estrogen neuroprotection: Role of transforming growth factor-α in estrogen-induced upregulation of glutamate transporters in astrocytes

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ABSTRACT

Extensive studies from the past decade have completely revolutionized our understanding about the role of astrocytes in the brain from merely supportive cells to an active role in various physiological functions including synaptic transmission via cross-talk with neurons and neuroprotection via releasing neurotrophic factors. Particularly, numerous studies have reported that astrocytes mediate the neuroprotective effects of 17β-estradiol (E2) and selective estrogen receptor modulators (SERMs) in various clinical and experimental models of neuronal injury. Astrocytes contain two main glutamate transporters, glutamate aspartate transporter (GLAST) and glutamate transporter-1 (GLT-1), that play a key role in preventing excitotoxic neuronal death, a process associated with most neurodegenerative diseases. E2 has been shown to increase expression of both GLAST and GLT-1 mRNA and protein and glutamate uptake in astrocytes. Growth factors such as transforming growth factor-α (TGF-α) appear to mediate E2-induced enhancement of these transporters. These findings suggest that E2 exerts neuroprotection against excitotoxic neuronal injuries, at least in part, by enhancing astrocytic glutamate transporter levels and function. Therefore, the present review will discuss proposed mechanisms involved in astrocyte-mediated E2 neuroprotection, with a focus on glutamate transporters.

Contents

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1. Introduction

Astrocytes are the most abundant, non-neuronal glial cells in the brain and participate actively in normal physiology as well as in acute injury and the pathological process of chronic neurological disorders in the central nervous system (CNS) (Hamby and Sofroniew, 2010; Ullian et al., 2004). The traditional understanding of astrocyte function as merely supporting cells of the brain has completely changed since the discovery that astrocytes are involved in various important functions in the CNS; these include the promotion of glutamate clearance, K^+ buffering, antioxidant defense mechanisms and neuronal excitability by coupling with neurons (Allen and Barres, 2009; Clarke and Barres, 2013; Svendsen, 2002; Zhang and Barres, 2010). Astrocytes are located in juxtaposition to neurons (which they outnumber 10:1 in some regions of the brain), and act as critical mediators of neuronal survival (Dhandapani and Brann, 2007). Besides maintaining neural tissue homeostasis in the brain, the multifunctional roles of astrocytes in the CNS have drawn significant attention to their potential as therapeutic targets for various neurological disorders (Barreto et al., 2011; Brann et al., 2007).

In addition to the importance of astrocytes, 17β-estradiol (E2) is now widely accepted to exert a broad spectrum of actions in the CNS including neuroprotection (Lee and McEwen, 2001; Wise, 2002). This is true for disorders such as multiple sclerosis (MS), schizophrenia, depression, Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) and acute ischemic stroke [reviewed in (Behl, 2002; Garcia-Segura et al., 2001; Green and Simpkins, 2000)]. Moreover, a growing body of evidence suggests that astrocytes are a major cellular target for this E2-induced neuroprotection (Azcoitia et al., 2010; Dhandapani and Brann, 2007; Sortino et al., 2005). Although the exact mechanism(s) involved in astrocyte-mediated E2 neuroprotection remain to be established, E2 increases the expression and function of the glutamate transporters in astrocytes, GLAST and GLT-1 (Lee et al., 2009a, 2012b). Since astrocytic glutamate transporters maintain optimal levels of glutamate in synaptic clefts, which prevents excitotoxic neuronal death, E2-induced enhancement of these transporters may be a crucial step leading to E2-induced neuroprotection. The fact that GLAST and GLT-1 do not contain an estrogen response element (ERE) in their promoters suggests that E2-induced upregulation of GLAST and GLT-1 is an indirect effect, mediated via activation of other cellular signaling pathways. Studies have shown that growth factors such as TGF-α and TGF-β are vital to this E2 action on glutamate transporters (Lee et al., 2009a, 2012b). Thus, the goal of this review is to shed light on the role of astrocyte-derived growth factors in E2 neuroprotection with a particular focus on mechanisms involved in E2-induced upregulation of astrocytic glutamate transporters, GLAST and GLT-1.

2. Role of astrocytes in E2 neuroprotection

It is well-documented that E2 promotes neuronal survival (Sudo et al., 1997 #156) and offers neuroprotection against various stimuli including iron (Vedder et al., 1999 #157), glutamate (Singer et al., 1996 #158), kainate (Regan and Guo, 1997 #160) and H_2O_2 (Bonnefont et al., 1998 #159) in neurons. However, it should be emphasized that astrocytes also play a critical role in mediating E2-induced neuroprotection as E2 is capable of exerting neuroprotection against a neuronal toxic insult in the presence of astrocytes under condition in which it is unable to protect neurons in the absence of astrocytes (Dhandapani and Brann, 2002 #10; Park et al., 2001 #11; Platania et al., 2005 #12). The most remarkable evidence for the role of astrocytes in E2-induced neuroprotection is a study by the Sofroniew group, revealing that E2 was unable to protect neurons against neuronal injuries in a model of experimental autoimmune encephalomyelitis (EAE, an animal model of MS) when ER-α was genetically knocked out in astrocytes, while it still exerted neuroprotection when neuronal ER-α was ablated (Spence et al., 2013 #115). On the other hand, several studies have reported that neuronal ER-α mediated E2 neuroprotection against middle cerebral artery occlusion (MCAO) in mice (Elzer et al., 2010 #161), glutamate neurotoxicity in hippocampal neurons (Gingerich et al., 2010 #44; Zhao and Brinton, 2007 #39). These results indicate that astrocytes might not be exclusively mediating E2-induced neuroprotection, but ample evidence reveals that astrocytes play a major role in this process (reviewed in (Dhandapani and Brann, 2007 #2;Mahesh et al., 2006 #234).

Astrocytes express all estrogen receptor (ER) subtypes including classical ER-α and ER-β as well as the G protein-coupled ER, GPR30 (Garcia-Segura et al., 1999; Kuo et al., 2010; Pawlak et al., 2005b). Among several proposed mechanisms for E2 neuroprotection involving astrocytes, an anti-inflammatory action in astrocytes appears to be critical to achieve E2-induced neuroprotection (Spence et al., 2011). Thus, E2 exerts neuroprotection against EAE in astrocytes by decreasing chemokine CCL2 and CCL7 levels (Spence et al., 2013). Since neuroinflammation is associated with many neurodegenerative diseases including MS, an E2-induced anti-inflammatory effect in astrocytes may likely contribute to E2 effects on neuroprotection as a whole (Vegeto et al., 2008). It also appears that inflammation is involved in the impairment of astrocytic glutamate transporters in neuropathological processes since proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) also reduce the glutamate transporter GLT-1 in astrocytes (Sama et al., 2008; Sitcheran et al., 2005; Su et al., 2003). Even though the exact mechanism involved in E2-induced enhancement of glutamate transporters in astrocytes remains to be established, is it clear that this pathway needs to be vigorously pursued, as it may yield therapeutic strategies for neurological disorders associated with excitotoxic neuronal injuries.

3. Role of astrocyte-derived growth factors in E2 neuroprotection

It has been well documented that E2 action in astrocytes leads to the synthesis and release of various growth factors including nerve growth factor (NGF), insulin-like growth factor 1 (IGF-1), basic fibroblast growth factor (bFGF), transforming growth factor (TGF)-α and TGF-β, brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF); all of these have been shown to exert neuroprotection (Buchanan et al., 2000; Duenas et al., 1994; Flores et al., 1999).

E2 increases NGF mRNA and protein levels in primary astrocytes (Xu et al., 2013) and exerts synergistic neuroprotective effects with NGF against apoptosis (Gollapudi and Oblinger, 1999). E2 also increases BDNF mRNA and protein expression in astrocytes and exerts neuroprotection via BDNF (Sohrabji and Lewis, 2006; Xu et al., 2013). Moreover, multiple *in vivo* studies have demonstrated that BDNF exerts neuroprotection against ischemic and traumatic brain injury (Beck et al., 1994; Kazanis et al., 2004; Yamashita et al., 1997). E2 also increases expression and secretion of GDNF in astrocytes (Xu et al., 2013), and GDNF protects NMDA-induced neuronal cell death by attenuating calcium influx through activation of the ERK pathway (Nicole et al., 2001). Another study has shown that E2 increases the production and release of GDNF in astrocytes and rescues spinal motoneurons from AMPA-induced excitotoxicity (Platania et al., 2005). IGF-1 signaling also has been reported to play a critical role in mediating E2 neuroprotection via astrocytes. E2 and IGF-1 receptors are often co-localized in