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Estrogen attenuates Manganese-induced glutamate transporter impairment in rat primary astrocytes

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Abstract

The astrocytic glutamate transporters (GLT-1, GLAST) are critical for removing excess glutamate from synaptic sites, thereby maintaining glutamate homeostasis within the brain. 17 -Estradiol (E2) is one of the most active estrogen hormones possessing neuroprotective effects both in *in vivo* and *in vitro* models, and it has been shown to enhance astrocytic glutamate transporter function (Liang et al. 2002; Pawlak et al. 2005). However, E2 is not clinically optimal for neuroprotection given its peripheral feminizing and proliferative effects; therefore, brain selective estrogen receptor modulators (neuroSERMs) (Zhao et al. 2005) that specifically target estrogenic mechanisms, but lack the systemic estrogen side effects offer more promising therapeutic modality for the treatment of conditions associated with excessive synaptic glutamate levels. This review highlights recent studies from our laboratory showing that E2 and SERMs effectively reverse glutamate transport inhibition in a manganese (Mn)-induced model of glutamatergic deregulation. Specifically, we discuss mechanisms by which E2 restores the expression and activity of glutamatergic neurotransmission. We advance the hypothesis that E2 and related compounds, such as tamoxifen (TX) may offer a potential therapeutic modality in neurodegenerative disorders, which are characterized by altered glutamate homeostasis.

Introduction

Although manganese (Mn) is an essential element required for normal development and for the proper function of multiple enzymes, such as Mn superoxide dismutase, arginase, and glutamine synthase (ASTDR 2000), chronic high levels of Mn exposure represent a toxicological concern (Aschner et al. 2009). Human exposures are commonly associated with battery manufacturing, water purification, as well as bactericidal and fungicide agents (de Tollenaer et al. 2006). Moreover, increased serum Mn levels are observed in chronic liver failure, as result of the inability to excrete the metal via the biliary system (McKinney et al. 2004), as well as in patients on total parenteral nutrition (Aschner and Aschner 2005).

While several tissues are affected by excessive Mn exposure, the central nervous system (CNS) is particularly vulnerable to its toxicity (Bowman et al. 2011). Long-term Mn exposures result in a neurologic syndrome referred to as *manganism*. Although *manganism*

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shares multiple clinical features with Parkinson's disease (PD) (Barbeau 1984; Sloot et al. 1994), the primary sites of damage following Mn neurotoxicity include the globus pallidus (GP) and striatum with the subtantia nigra pars compacta (SNc) generally spared (Olanow 2004). Globus pallidus (GP) neurons have been shown to be selectively vulnerable to Mn intoxication (Gwiazda et al. 2002) with marked neuronal loss and astrocytosis, particularly in the medial segment. The GP contains abundant -aminobutyric acid (GABA) projections (Pal et al. 1999), and the degeneration of these GABAergic neurons leads to decreased inhibitory GABA input to the subthalamic nucleus. Thus, Mn dysinhibits glutamate output to the subtantia nigra (SN) resulting in chronic over-stimulation of dopaminergic (DAergic) neurons (Verity 1999). The exacerbation of dopamine neurotransmission is associated with oxidative stress, which may hasten Mn neurotoxicity; a less severe degeneration occurs in the putamen, the caudate nucleus and substantia nigra pars reticulata (SNr) (Yamada et al. 1986).

Mn preferentially accumulates in astrocytes where it is known to impair glutamate transporter function (Erikson and Aschner 2002; Hazell and Norenberg 1997). There is compelling evidence of glutamate-mediated excitotoxicity in Mn neurotoxicity, and the involvement of astrocytic glutamate transporters in this process (Aschner et al. 1992; Danbolt 2001). Mn injection into the rat striatum induces excitotoxic lesions and pre-treatment with the noncompetitive *N*-methyl D-aspartate (NMDA) antagonist, MK801, blocks these lesions (Brouillet et al. 1993). Furthermore, Mn decreases astrocytic glutamate uptake (Hazell and Norenberg 1997; Normandin and Hazell 2002) and expression of the astrocytic glutamate transporters, GLAST (EAAT1 in human) (Erikson and Aschner 2002) and GLT-1 (EAAT2 in human) (Deng et al. 2012). Although the molecular mechanisms involved with Mn-induced glutamate dyshomeostasis are not fully understood, recent evidence shows that protein kinase C (PKC) activation is one of the key events in mediating decreased glutamate uptake into astrocytes upon Mn exposure (Sidoryk-Wegrzynowicz et al. 2011).

The neuroprotective effect of 17 -Estradiol (E2) and SERMs is partially mediated by astrocytes

Epidemiological and experimental studies have reported gender effects on the development of specific neuropathologic conditions, including metal-induced neurotoxicity (Beuter et al. 1999; Dorman et al. 2004; Malagutti et al. 2009). In this regard, several studies established that 17 -estradiol (E2), at physiological concentrations, exerts protective effects in a number of neurodegenerative disorders, such as Alzheimer’s disease (AD), PD and acute ischemic stroke (Dhandapani and Brann 2007). Selective estrogen receptor modulators (SERMs) have been in clinical use for the treatment and/or prevention of breast cancer (tamoxifen; TX) and osteoporosis (raloxifene). Both these SERMs are neuroprotective in various *in vivo* and *in vitro* models of neurological disorders (Biewenga et al. 2005; Kimelberg et al. 2000). E2 exerts neuroprotective effects both via estrogen receptor (ER)-dependent and -independent mechanisms (Manthey and Behl 2006). Lee and colleagues have demonstrated that E2 protects against Mn-induced oxidative stress and cell death both in neurons and astrocytes (Lee et al. 2009a). While E2 may have a direct protective effect on neurons, emerging evidence points to the astrocytes as key mediators of its effect (Dhandapani et al. 2003; Dhandapani et al. 2005; Sortino et al. 2004; Wilson et al. 2000). Notably, astrocytes express several subtypes of the estrogen receptors (ERs), including ER-α and ER-β, as well as G protein-coupled receptor 30 (GPR30). Although the classical ERs are recognized as the nuclear receptors, E2 also exerts non-classical effects via the plasma membrane-associated ERs. The latter effects are mediated via MAPK/ERK and PI3K/Akt signaling (Dhandapani and Brann 2007). ER- in astrocytes, but not in neurons, appears responsible for E2-induced neuroprotection in experimental autoimmune encephalomyelitis (EAE) (Spence et al. 2011).

GPR30 mediated neuroprotection has been invoked in ischemic animal model (Lebesgue et al. 2010). Astrocytes may also contribute to neuroprotection by increasing local estrogen levels via the activation of aromatase, which catalyzes the synthesis of E2 from testosterone (Azcoitia et al. 2001; Gulinello et al. 2006). Astrocytes are also an important source of E2-induced trophic factors, which possess neuroprotective functions. For example, in response to treatment with E2, astrocytes upregulate the expression of growth factors, such as transforming growth factor alpha (TGF-α) and TGF- 1(Fig. 1) (Dhandapani et al. 2003; Duenas et al. 1994; Mahesh et al. 2006). Tamoxifen (TX), acting as an antagonist of the ERs in breast tissue, has been shown to evoke neuroprotective effects by increasing TGF- 1 synthesis in astrocytes (Dhandapani and Brann 2003a). E2 increases the expression of the astroglial glutamate transporters, GLAST and GLT-1, thus reducing extracellular glutamate levels (Fig. 1) (Pawlak et al. 2005). E2 also enhances astroglial glutamate transporter GLAST functions by modulating the trafficking/redistribution of glutamate transporters (Lee et al. 2009b).

Astrocytic glutamate transporters, neurodegeneration and neuroprotection

Glutamate is the major excitatory neurotransmitter in the mammalian CNS. As such, glutamate plays an important role in many CNS functions (Muller et al. 1994) and a number of neurodegenerative diseases have been associated with glutamate transporter impairment, including amyotrophic lateral sclerosis (ALS), AD and PD (Masliah et al. 2000; Sheldon and Robinson 2007). Optimal synaptic glutamate concentrations are regulated mainly by GLAST (Storck et al. 1992) and GLT-1 (Pines et al. 1992), both of which are predominantly localized in astrocytes (Rothstein et al. 1996). In optimal physiological conditions, astrocytes are responsible for neuronal activity regulation and removal of glutamate from the synaptic cleft (80% of Glutamate released from neurons is taken up by astrocytes) (de Vivo et al. 2010). While GLAST is highly expressed in cultured primary astrocytes, GLT-1 is abundantly expressed *in vivo*, playing a critical role in taking up glutamate from the synaptic cleft. GLT-1 expression in astrocyte cultures is regulated by neuronal factors (Gegelashvili et al. 1997; Schlag et al. 1998; Swanson et al. 1997). Despite the crucial role of astrocytic glutamate transporters in the maintenance of glutamate homeostasis, molecular details regarding the regulation of glial glutamate transporters has yet to be fully understood. In addition to genomic regulation of transporter expression (Figiel et al. 2003), glutamate transporter GLT-1 is also regulated by post-transcriptional mechanisms (Beart and O'Shea 2007; Robinson 2002). Another mechanism invoked for glutamate transporter regulation is trafficking of transporters in response to activation of a variety of signaling molecules, such as PKC and phosphoinositide-3-kinase (PI3K/Akt) (Danbolt 2001; Guillet et al. 2005; Sims et al. 2000).

Since impairment in astrocytic glutamate transporter expression and function represents the key contributing factor to neural pathogenesis, several experimental approaches have been pursued for neuroprotection by enhancing glutamate transporter function. These include transgenic mouse models over-expressing glutamate transporters, pharmacological upregulation of glutamate transporters, as well as transduction of various cell types with exogenous glutamate transporters using viral vectors (Zhou and Sutherland 2004). GLT-1 over-expressing mice exhibit reduced neurological signs of ischemia (Romera et al. 2007). Several approaches have also been advanced in search for novel therapeutic strategies for small molecules that might regulate expression or function of glutamate transporters (Dunlop 2006). -Lactam antibiotics stimulate GLT-1 expression and have been shown to be efficacious both *in vitro* and *in vivo* in a mouse model of ALS (Rothstein et al. 2005). Other studies have established that up-regulation of GLT-1 is neuroprotective in models of ALS and cerebral ischemia (Chu et al. 2007; Ganel et al. 2006).

Do growth factors play a role in the E2-enhancing glutamate transporter function in astrocytes?

E2 increases expression of certain growth factors such as transforming growth factor- (TGF- , transforming growth factor- 1 (TGF- 1) and basic fibroblast growth factor (bFGF) in astrocytes (Dhandapani et al. 2005; Ojeda et al. 2006; Siegel and Chauhan 2000) (Fig. 1). E2 has been shown to protect neurons by increasing the expression of astrocytic TGF- 1 in several neurological experimental models, including AD and ischemia (Fig. 1) (Dhandapani et al. 2003; Tesseur et al. 2006; Wyss-Coray 2004). TGF- binds to the EGFR with high affinity (Gomez-Pinilla et al. 1988; Planas et al. 1998) and reduces infarct volume after focal ischemia (Justicia et al. 2001; Justicia and Planas 1999). TGF acts primarily on astrocytes (Junier 2000; Schluter et al. 2002) and the expression of GLAST and GLT-1 is stimulated by EGF/TGF- (Figiel and Engele 2000; Zelenaia et al. 2000) and bFGF (Suzuki et al. 2001) in cultured cortical astrocytes (Fig. 1).

Mn neurotoxicity involves impairment of glutamate transporters, which contributes to pathological neuronal degeneration in the GP and striatum. Although astrocytes are the main cellular target of Mn and E2/SERM-neuroprotection, the mechanisms underlying this effect in Mn-induced glutamate transporter impairment have yet to be fully established. TGF- may play an important role in E2/TX-induced reversal of Mn-impaired GLT-1 expression, given our findings that E2 and TX enhanced GLT-1 function by increasing TGF-α expression, thus, attenuating Mn-induced impairment in astrocytic GLT-1 expression and glutamate uptake (Lee et al. 2012a). Moreover, this E2/TX action was associated with GLT-1 gene expression levels, activating the GLT-1 promoter. Our findings also reveal that TGF- plays an intimate role in E2/TX-induced GLT-1 expression, given that knockdown of TGF-α abolished the E2/TX effect on GLT-1 expression and GLT-1 promoter activity (Lee et al. 2012a). The effect of E2/TX on TGF-α mRNA and protein levels with a concomitant increase in astrocytic glutamate uptake was mediated by the activation of MAPK/extracellular signal-regulated kinase (ERK) and PI3K/Akt signaling pathways (Lee et al. 2012a). We further demonstrated that ERs (ER-α, ER-β, and G protein-coupled receptor 30) were involved in mediating the effects of E2 on the regulation of TGF-α, GLT-1, and glutamate uptake (see Fig. 1 for additional details).

Transcriptional regulation of E2-induced GLT-1 expression via GPR30

Although the classical ERs, ER- and ER- upregulate GLT-1 expression recent studies in our laboratory indicate that GPR30, also known as a G-protein coupled estrogen receptor 1 (GPER), is critically involved in regulating the E2-induced GLT-1 expression (Lee et al. 2012b). This is supported by results in which blocking GPR30 function fully abrogates the effect of G-1, a selective GPR30 agonist, on GLT-1 protein expression. The GPR30-induced increase in GLT-1 expression is mediated at the transcriptional level, via activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- B) and CREB) pathways. The promoter of the GLT-1 gene contains *cis*-elements of NF- B and CREB binding sites. The NF- B pathway appears to play a critical role, given that GPR30 not only transactivated EGFR, which is known to regulate GLT-1 expression through NF- B pathway (Ghosh et al. 2011; Sitcheran et al. 2005), but also induced the expression of TGF- , a ligand of EGFR. The NF- B pathway is intimately involved in the G-1-induced enhancement of GLT-1 expression. Both NF- B p50 and NF- B p65, which compose the predominant heterodimer form of NF- B in the brain (Meffert and Baltimore 2005) are involved in G-1-induced GLT-1 regulation, supported by the observation that G-1 induced the binding of these two subunits (p50 and p65) to the *cis*-element of GLT-1 promoter and activated the NF- B luciferase reporter. The CREB pathway might be another pathway that mediates GPR30-induced GLT-1 expression. G-1/GPR30 activates the G protein-coupled receptor

system and the downstream to the cAMP/PKA pathways; furthermore it induces CREB binding to a cAMP response element (CRE) site in the GLT-1 promoter (Lee et al. 2012b). Taken together, these results suggest that E2/TX enhance astrocytic glutamate transporter expression via increased transforming growth factors (both TGF-α and TGF- 1 expression). Furthermore, both E2 and TX effectively reverse Mn-- induced glutamate transport inhibition by restoring its expression and activity, thus offering a potential therapeutic modality in neurodegenerative disorders characterized by altered glutamate homeostasis.

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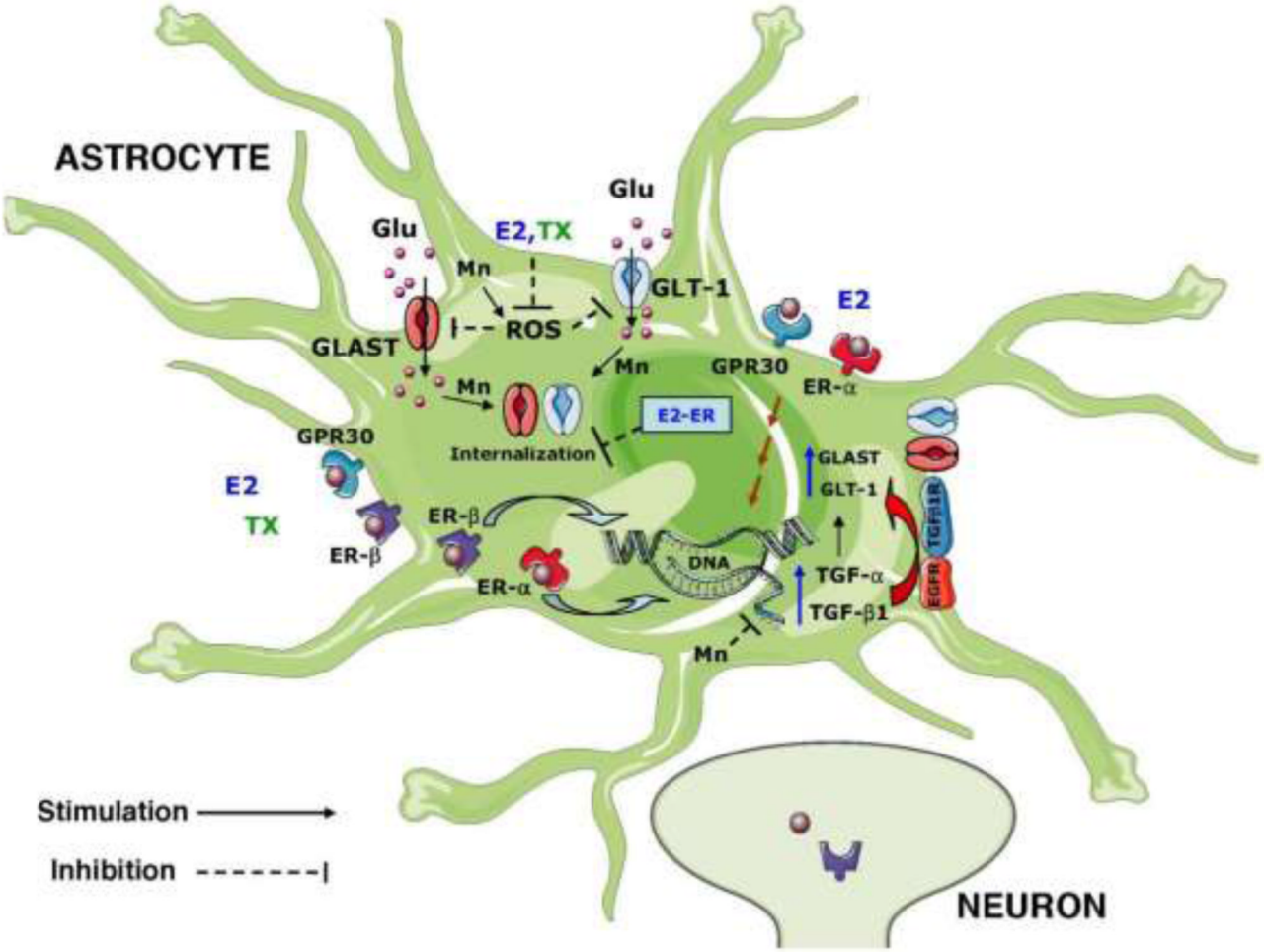

Fig. 1.

Putative mechanism associated with the effect of E2/TX on GLT-1 and GLAST expression. GLT-1 expression is increased by treatment with E2/TX in astrocytes. The effect is mediated via the nuclear ER (ER-α and ER-β) as well as GPR30. GPR30 is localized on the plasma membrane and/or endoplasmic reticulum. E2 and TX induce TGF-α as well as TGF-1. These, in turn, bind to EGFR or TGFR with high affinity and activate TGF- 1 by autocrine/paracrine modes. TGF- 1 mediates the effects of E2/TX on GLT-1 (as well as GLAST) expression by multiple signaling pathways, including EGFR (PI3K, mitogen-activated protein kinase (MAPK), and protein kinase A (PKA) -not shown). Glu: glutamate; GLT-1: glutamate transportert-1; GLAST: glutamate aspartate transporter; ER, estrogen receptor; GPR30, G protein-coupled Receptor 30; TGF 1 R: Receptor for TGF- 1; EGFR: Receptor for TGF- .