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Research Report

Estradiol pretreatment ameliorates impaired synaptic plasticity at synapses of insulted CA1 neurons after transient global ischemia

*Koichi Takeuchi, Yupeng Yang[1], Yukihiro Takayasu[2], Michael Gertner, Jee-Yeon Hwang, Kelly Aromolaran, Michael V.L. Bennett, R. Suzanne Zukin**

Dominick P. Purpura Department of Neuroscience, Rose F. Kennedy Center for Research in Mental Retardation and Developmental Disabilities, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461, USA

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ABSTRACT

Global ischemia in humans or induced experimentally in animals causes selective and delayed neuronal death in pyramidal neurons of the hippocampal CA1. The ovarian hormone estradiol administered before or immediately after insult affords histological protection in experimental models of focal and global ischemia and ameliorates the cognitive deficits associated with ischemic cell death. However, the impact of estradiol on the functional integrity of Schaffer collateral to CA1 (Sch-CA1) pyramidal cell synapses following global ischemia is not clear. Here we show that long term estradiol treatment initiated 14 days prior to global ischemia in ovariectomized female rats acts *via* the IGF-1 receptor to protect the functional integrity of CA1 neurons. Global ischemia impairs basal synaptic transmission, assessed by the input/output relation at Sch-CA1 synapses, and NMDA receptor (NMDAR)-dependent long term potentiation (LTP), assessed at 3 days after surgery. Presynaptic function, assessed by fiber volley and paired pulse facilitation, is unchanged. To our knowledge, our results are the first to demonstrate that estradiol at near physiological concentrations enhances basal excitatory synaptic transmission and ameliorates deficits in LTP at synapses onto CA1 neurons in a clinically-relevant model of global ischemia. Estradiol-induced rescue of LTP requires the IGF-1 receptor, but not the classical estrogen receptors (ER)-α or β. These findings support a model whereby estradiol acts *via* the IGF-1 receptor to maintain the functional integrity of hippocampal CA1 synapses in the face of global ischemia.

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*Corresponding author. fax: +1 718 430 8932.
E-mail address: suzanne.zukin@einstein.yu.edu (R.S. Zukin).
[1]Present address: University of Science and Technology of China, Hefei, China.
[2]Present address: Department of Otolaryngology, Gunma University, Maebashi, Japan.

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1. Introduction

Transient global ischemia arising in humans as a consequence of cardiac arrest or induced experimentally in animals causes selective and delayed neuronal death and in many cases delayed onset of cognitive deficits (Liou et al., 2003; Moskowitz et al., 2010; Ofengeim et al., 2011; Etgen et al., 2011; Inagaki and Etgen, 2013). Pyramidal neurons in the hippocampal CA1 are particularly vulnerable. Histological evidence of neuronal death is not observed until 2 days after insult. During the ischemic episode, cells exhibit a transient, early rise in intracellular Ca^{2+}, depolarize and become inexcitable. After reperfusion, cells appear morphologically normal, exhibit normal intracellular Ca^{2+} and regain the ability to generate action potentials for 24-72 h after the insult (Liou et al., 2003; Moskowitz et al., 2010; Ofengeim et al., 2011). Ultimately, there is a late rise in intracellular Ca^{2+} and Zn^{2+}, and death of CA1 pyramidal neurons ensues, exhibiting hallmarks of apoptosis and necrosis. The substantial delay between insult and neuronal death is consistent with the possibility of therapeutic intervention.

Estradiol, the primary estrogen produced and secreted by the ovaries, has widespread actions in the brain. Estradiol and related ovarian steroids modify the structure and function of hippocampal neurons. Estradiol enhances spine density (Hao et al., 2006; Srivastava et al., 2008; Smith et al., 2009) and synapse number (Yankova et al., 2001; Ma et al., 2010) on pyramidal cells in the hippocampal CA1. Consistent with this, estradiol enhances synaptic NMDA receptor (NMDAR) currents and enhances the magnitude of NMDAR-dependent long-term potentiation (LTP) at Schaffer collateral to CA1 (Sch-CA1) pyramidal cell synapses in the hippocampus under physiological conditions (Montoya and Carrer, 1997; Bi et al., 2001; Gupta et al., 2001; Smith and McMahon, 2005, 2006; Smejkalova and Woolley, 2010; Snyder et al., 2011). It is likely that these actions of estrogen facilitate the enhanced learning and memory observed in rats, primates and humans in response to estrogen replacement.

The classical estrogen receptors ERα and ERβ are expressed throughout the brain. In hippocampus, ERα and ERβ are expressed primarily on inhibitory interneurons (for review, see Woolley, 2007; Lebesgue et al., 2009; Etgen et al., 2011; Inagaki and Etgen, 2013; Baudry et al., 2013). Estrogens produce their actions on neurons, at least in part, *via* binding to ERα and ERβ. Ligand activation of ERα and ERβ promotes release of heat-shock protein, estrogen receptor dimerization and formation of an activated transcription factor which recognizes Estrogen Response Elements within the promoters of target genes. In addition to its genomic actions, estrogens promote rapid nongenomic signaling events in cells by engaging intracellular pathways such as ERK/MAPK, PI3K/Akt and JAK/STAT signaling (Lebesgue et al., 2009; Micevych and Kelly, 2012). These actions may be mediated, at least in part, by GPR30, a member of the seven transmembrane superfamily of G protein-coupled receptors with high affinity for estradiol and related estrogens (for review, see Lebesgue et al., 2009; Etgen et al., 2011; Micevych and Kelly, 2012). Activation of GPR30 by estradiol stimulates production of cAMP, mobilization of intracellular Ca^{2+} and activation of growth factor signaling.

Estradiol and IGF-1 act synergistically in neurons to regulate synaptic remodeling, neuronal differentiation and neuronal survival (Lebesgue et al., 2009; Garcia-Segura et al., 2010). IGF-1 receptors are critical to estradiol protection of hilar neurons from seizure-induced injury (Azcoitia et al., 1999). In the brain, estradiol and IGF-1 activate ERK/MAPK (Lebesgue et al., 2009; Etgen et al., 2011; Inagaki and Etgen, 2013), a well-characterized intracellular signaling cascade implicated in neuronal plasticity and survival (Sweatt, 2004; Thomas et al., 2005; Lebesgue et al., 2009). Upon stimulation with estradiol, ERα and the IGF-1 receptor form a macromolecular signaling complex, which recruits and activates downstream kinases including MAPK (Kahlert et al., 2000; Mendez et al., 2003; Song et al., 2004; Jover-Mengual et al., 2007). ERK/MAPK signaling culminates in phosphorylation and activation of nuclear transcription factors such as signal transducer and activator of transcription-3 (STAT3) (Sehara et al., 2013) and cAMP-response element binding protein (CREB) (Boulware et al., 2013), which regulate expression of target genes important to neuronal survival and protection.

Whereas a single, acute injection of estradiol administered immediately prior to or after ischemia at supraphysiological levels affords protection against ischemia-induced impairment of synaptic plasticity and hippocampal-based behavior in animal models of global ischemia (Sandstrom and Rowan, 2007; Inagaki et al., 2012; Dai et al., 2013), the impact of chronic estradiol administration at near physiological concentrations is, as yet unknown. Whereas long term administration of estradiol at physiological doses prior to insult ameliorates neuronal death (Plamondon et al., 1999; Jover et al., 2002; Miller et al., 2005; Jover-Mengual et al., 2007) and cognition (Gulinello et al., 2006; De Butte-Smith et al., 2009) in global ischemia, its impact on synaptic transmission and synaptic plasticity are not well-delineated.

The present study was undertaken to examine the impact of long term estradiol pretreatment at physiological doses on the functional integrity of hippocampal CA1 pyramidal neurons in a clinically-relevant model of global ischemia. We show for the first time that estradiol acts *via* IGF-1 receptors to ameliorate ischemia-induced deficits in NMDAR-dependent LTP at Sch-CA1 synapses in acute hippocampal slices from animals subjected to transient global ischemia. The IGF-1 antagonist JB-1 reverses the neuroprotective effects of estradiol on both synaptic transmission and synaptic plasticity. These findings suggest that estradiol and IGF-1 act in a coordinated manner to maintain the functional integrity of CA1 neurons in the face of global ischemia.

2. Materials and methods

2.1. Animals

Six-week old female Sprague Dawley rats weighing 100–150 g (Charles River, Wilmington, DE) at the time of ischemic insult were housed and maintained in a temperature- and light-controlled environment with a 12/12-h light/dark cycle in a facility at the Institute for Animal Studies at the Albert Einstein College of Medicine. All animal experiments were carried out in accordance with the principles and guidelines of the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Protocols used for this study were