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Estrogens as neuroprotectants: Estrogenic actions in the context of cognitive aging and brain injury

Q1 E.B. Engler-Chiurazzi [a,b,*], C.M. Brown [a,c], J.M. Povroznik [a,d], J.W. Simpkins [a,b]

Q2 [a] Center for Basic and Translational Stroke Research, West Virginia University, Morgantown, WV 26506, United States
[b] Department of Physiology and Pharmacology, West Virginia University, Morgantown, WV 26506, United States
[c] Department of Neurobiology and Anatomy, West Virginia University, Morgantown, WV 26506, United States
[d] Department of Pediatrics, West Virginia University, Morgantown, WV 26506, United States

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ABSTRACT

There is ample empirical evidence to support the notion that the biological impacts of estrogen extend beyond the gonads to other bodily systems, including the brain and behavior. Converging preclinical findings have indicated a neuroprotective role for estrogen in a variety of experimental models of cognitive function and brain insult. However, the surprising null or even detrimental findings of several large clinical trials evaluating the ability of estrogen-containing hormone treatments to protect against age-related brain changes and insults, including cognitive aging, stroke, and traumatic brain injury, led to hesitation by both clinicians and patients in the use of exogenous estrogenic treatments for nervous system outcomes. That estrogen-containing therapies are used by tens of millions of women for a variety of health-related applications across the lifespan has made identifying conditions under which benefits with estrogen treatment will be realized an important public health issue. Here we provide a summary of the biological actions of estrogen and estrogen-containing formulations. We have devoted special attention to highlighting the notion that estrogen appears to be a conditional neuroprotectant whose efficacy is modulated by several interacting factors. By developing criteria standards for desired beneficial peripheral and neuroprotective outcomes among unique patient populations, we can optimize estrogen treatments for attenuating the consequences of, and perhaps even preventing, cognitive aging Q4 and brain injury.

Contents

Abbreviations: 3NPA, 3-nitropropionic acid; 17αE2, 17 alpha-estradiol; 17βE2, 17 beta-estradiol; ATP, adenosine triphosphate; BBB, blood brain barrier; BDNF, brain-derived neurotrophic factor; BrdU, bromodeoxyuridine; CA, Cornu ammonis; CBF, cerebral blood flow; CCL2, chemokine ligand 2; CEE, conjugated equine estrogens; ChAT, choline acetyltransferase; CNS, central nervous system; DG, dentate gyrus; DMP/DMS, delayed match to position/delayed match to sample; DPN, diarylpropionitrile; E1, estrone; E3, estriol; ELITE, Early Versus Late Intervention Trial with Estradiol; eNOS, endothelial nitric oxide synthase; ER, estrogen receptor; ERα, estrogen receptor-α; ERβ, estrogen receptor-β; ERE, Estrogen Response Element; ET-1, endothelin-1; GPER1, G protein-coupled ER 1 (or GPR30); HT, hormone therapy; IGF, insulin-like growth factor; iNOS, inducible nitric oxide synthase; KEEPS, Kronos Early Estrogen Prevention Cognitive and Affective Study; KO, knock out; LTP, long term potentiation; MCAO, middle cerebral artery occlusion; MM, morris water maze; MPA, medroxyprogesterone acetate; mRNA, messenger RNA; NGF, nerve growth factor; NADPH, nicotinamide adenine dinucleotide phosphate; NMDA, N-methyl-D-aspartate; OC, oral contraceptive; Ovx, ovariectomy; pMCAO, permanent MCAO; Premarin®, CEE; Prempro®, CEE + MPA; PPT, propylpyrazole triol; RAM, radial arm maze; RNA, ribonucleic acid; ROS, reactive oxygen species; SERMs, Selective Estrogen Receptor Modulators; STAIR, stroke therapy academic industry roundtable; SVZ, subventricular zone; TBI, traumatic brain injury; TJ, tight junction; tMCAO, transient MCAO; TNFα, tumor necrosis factor alpha; tPA, tissue plasminogen activator; VCD, vinylcyclohexene diepoxide; WEST, Women's Estrogen for Stroke Trial; WHI, Women's Health Initiative; WHIMS, WHI Memory Study; WHIMS-Y, WHIMS of Younger Women; WT, wild type.

Q3 * Corresponding author at: Center for Basic and Translational Stroke Research, West Virginia University, Morgantown, WV 26506, United States.
E-mail addresses: elengler@hsc.wvu.edu (E.B. Engler-Chiurazzi), cmbrown@hsc.wvu.edu (C.M. Brown), jpovrozn@mix.wvu.edu (J.M. Povroznik), jwsimpkins@hsc.wvu.edu (J.W. Simpkins).

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1. Introduction: the role of estrogen beyond the gonads

Q5 Our current understanding of the biological role of the sex hormone estrogen and more broadly, the field of women's health, has its origins in the avian testis. Indeed, in 1849, the physiologist Arnold Adolf Berthold reported on his findings regarding the anatomical and behavioral consequences of testicular removal and transplantation in roosters (Berthold, 1849). In an elegantly designed experiment, Berthold subjected cockerels to full or partial testicular removal. Among animals in which both testes were excised, physiology and behavior was markedly altered in that "*they were not aggressive, they fought other cockerels rarely and in a half-hearted manner, and developed the monotone voice of the capon*". Yet, in birds that had only one testis removed or in castrated birds who received testicular transplantation, he noted that behavior remained indiscernible from that of a normal rooster, with these birds still crowing, fighting, and displaying the "*usual reactions to hens*". Given that the transplanted testes did not always re-establish nerve connections within the rooster, Berthold attributed these findings to "*some productive function of the testes... by their action on the blood stream, and then by corresponding reaction of the blood on the entire organism, of which, it is true, the nervous system represents a considerable part*." Thus, whether Berthold realized the impact of his discovery or not, this experiment provided some of the first empirical support for the influence of sex hormones on the body and brain.

Characterizing the physiological impacts of estrogen is as important today as it was in Berthold's era. Nearly half of the global population is female, and sex-specific shifts in endogenous hormone levels related to cyclicity, pregnancy, and menopause are associated with differences in cognitive performance as well as altered risk for, and outcome from, neurological insults (Kimura, 2002; Kittner et al., 1996; Lisabeth and Bushnell, 2012; Workman et al., 2012). Further, today tens of millions of women use estrogen-containing treatments for many reasons ranging from menstrual cycle regulation to contraception to the amelioration of symptoms associated with the menopausal transition (Hersh et al., 2004; Jones et al., 2006). Although numerous reports note a multitude of beneficial neuroprotective effects of estrogens (reviewed in Acosta et al., 2013; Arevalo et al., 2015; Brown, 2009; Luine, 2014; Simpkins and Singh, 2008), the use of estrogenic compounds is controversial. Indeed, the known increased risk of stroke associated with oral contraceptive (OC) use coupled with the surprising null or even detrimental findings of the large, double-blind, placebo-controlled Women's Health Initiative (WHI) clinical trial regarding the risk for adverse outcomes among post-menopausal women taking hormone therapy (HT) led to hesitation by both clinicians and patients in the use of exogenous estrogen-containing treatments for brain-related outcomes (Kittner et al., 1996; Manson et al., 2013). Thus, there is a pressing medical need to understand the conditions under which estrogens exert neuroprotection.

Here, we review the literature regarding the nature of neuroprotection by estrogen and estrogen-containing compounds among females. We limited this discussion to studies in which human participants, rodent subjects, or in vitro cultures were utilized to assess the effects of 'estrogen' within the context of cognition, stroke, and traumatic brain injury (TBI). Our strategy for selection of published articles for citation in the current review is defined by the inclusion of studies in which a finding was first demonstrated, as well as seminal papers describing key caveats within a given field of research. In areas of research where the number of published studies is limited (for example, the cognitive impacts of estrone; E1), we made efforts to include all work conducted. Whenever possible, references included are primary research articles although we have also directed readers to several thorough and key reviews exhaustively addressing topics beyond the scope of the current discussion. For instance, neuroprotective actions of estrogens, and the complex mechanisms underlying these effects, have been documented in several domains of neurological function, injury, and disease (Chakrabarti et al., 2014), such as the experimental autoimmune encephalomyelitis model of multiple sclerosis (Offner and Polanczyk, 2006), spinal cord injury (Elkabes and Nicot, 2014) and Parkinson's Disease

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