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Review

Estrogen and cerebrovascular regulation in menopause

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ABSTRACT

Estrogen (E2), classically viewed as a reproductive steroid hormone, has non-reproductive functions throughout the body including in the brain and vasculature. Studies report diminished neuroprotection with declining E2 levels, corresponding with higher incidence of cerebrovascular and neurological disease. However, the effects of menopausal hormone therapy (MHT) on the cerebral vasculature and brain function remain controversial. This review will focus on evidence of 17β-estradiol actions in the cerebral vasculature, with a particular emphasis on the vasoactive, anti-inflammatory, anti-oxidant, metabolic and molecular properties. Controversies surrounding MHT in relation to cerebrovascular disease and stroke risk will be discussed, particularly the emerging evidence from clinical trials supporting the critical period hypothesis of estrogen protection.

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1. Introduction

The brain is the most highly perfused organ in the body, consisting of specialized vascular beds that sustain metabolic needs of cellular structures (Cipolla et al., 2009). Autoregulatory mechanisms of the cerebral circulation assure efficient perfusion by responding to changes in perfusion pressure. Physiological processes regulating cerebral blood flow (CBF) include perivascular nerve constriction or arterial dilation (Drake and Iadecola, 2007), arterial diameter modifications by astrocyte end feet (Gordon et al., 2007) and endothelial release of hemodynamic and vasoactive elements (Faraci and Heistad, 1998). In addition, a distinct and selective microenvironment known as the blood brain barrier (BBB) separates the brain from the peripheral circulation. The BBB consists of cerebral microvascular endothelium, astrocytes, pericytes, neurons and extracellular matrix, which altogether forms the "neurovascular unit" (Hawkins and Davis, 2005). These distinct cerebrovascular structures are particularly susceptible to aging pathophysiology and neurological damage (Cipolla et al., 2009; Duckles and Krause, 2007).

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Estrogen (17β-estradiol or E2), classically known as a reproductive steroid hormone, may function as a neurosteroid in the brain, given its neuroactive properties. In addition to regulation of gonadotropin releasing hormone (GnRH) release from the hypothalamus (Kenealy et al., 2013), *de novo* synthesis of E2 from testosterone via aromatase within the brain suggest broader neurosignaling capacity for the hormone (Balthazart and Ball, 2006; Hojo et al., 2004; Krause et al., 2011; McEwen et al., 2012; Saldanha et al., 2011). E2 synthesis may occur in the arterial wall of vascular smooth muscle cells directly, thus providing localized E2 effects and neuroprotection. Aromatase knockout (AKO) animals experience significantly greater ischemic damage as compared to controls, with E2 administration entirely reversing the knockout phenotype (McCullough et al., 2003). Although systemic contributions of E2 to peripheral vascular physiology have also been extensively studied (White, 2002; Babiker et al., 2002; Smiley and Khalil, 2009), the contribution of E2 in modifying cerebrovascular function in women throughout the aging process remains to be elucidated.

As women age, a permanent loss in ovarian follicles results in the sharp decline in circulating 17β-estradiol (E2) and estrone (E1) levels (Simpson and Davis, 2001; Trevoux et al., 1986) associated, in part, with the onset of menopausal symptoms. Animal studies and human clinical trials have shown that a state of E2 depletion promotes secondary changes in metabolic parameters, thus resulting in a higher prevalence of strokes, which may lead to vascular dementia and Alzheimer's disease. This review will focus on two important aspects underlying E2 actions in the brain during menopause. First, the molecular actions of E2 in the cerebral vasculature will be discussed, with a particular emphasis on vascular tone regulation, inflammation and mitochondrial bioenergetics. Second, clinical evidence and controversies in the field will be presented on the contributions of menopausal hormone treatment (MHT) to cerebrovascular risks and benefits. Examples from ischemic injury models and clinical stroke outcomes will be utilized to provide insight to E2 function in disease pathology.

1.1. Mechanisms of E2 and cerebral vascular regulation

The cerebral vasculature contributes to sexually dimorphic neurovascular diseases (Bushnell et al., 2006). Evidence supports neuroprotective, anti-inflammatory, vasodilatory and metabolic effects of E2 on cerebral blood vessels (Duckles and Krause, 2007; Miller and Duckles, 2008). The loss of E2 is thought to promote neurovascular disease in postmenopausal women and worsen stroke outcomes and has been associated with cognitive decline (Henderson and Lobo, 2012). The following sections will highlight the multifactorial and atheroprotective actions of E2, focusing on the positive and negative experimental data in the following areas: (1) cerebrovascular control of myogenic tone, (2) anti-inflammatory actions and generation of cytokines and (3) mitochondrial bioenergetics and free radical production.

1.1.1. Estrogen receptor-mediated mechanisms of cerebrovascular protection

Receptors for the sex steroids, including E2, are present in the cerebral vasculature, serving as a direct receptor-operated target by which hormonal actions are mediated. These receptor signals act through genomic and non-genomic processes to induce vasodilation, anti-inflammatory and anti-oxidant effects within cerebral blood vessels (Duckles and Krause, 2011). Both estrogen receptor (ER) α and ERβ isoforms are localized within endothelial cells, with ERα-specific localization in vascular smooth muscle cells (VSMCs) of cerebral arteries (Dan et al., 2003; Stirone et al., 2003). Molecular techniques demonstrate ERα upregulation in cerebrovascular arterial walls of ovariectomized rats with E2 treatment, with concomitant upreglation of endothelial nitric oxide synthase (eNOS) and nitric oxide (NO)-dependent vasodilation (Stirone et al., 2003). In contrast to ERα, ERβ mRNA expression increases in vascular endothelial and smooth muscle cells after vascular injury (Lindner et al., 1998). The ERβ isoform has been found in the nuclei of cerebral vascular endothelial cells (Tu and Jufri, 2013) and in VSMC (Hodges et al., 2000). Moreover, ERβ activation has also been implicated to reduce blood brain barrier (BBB) breakdown and vasogenic edema following cerebral ischemia in studies of an ERβ-selective agonist (Shin et al., 2013). Yet evidence from ERβ knockout studies suggests that this receptor subtype is unnecessary to preserve E2-mediated cerebrovascular protection (Karas et al., 1999). The discovery of a novel membrane-bound G-protein-coupled estrogen receptor-1 (GPER-1/GPR30) and its regulation by E2 provide additional support for the vasoprotective actions of E2 through rapid signaling. Studies using the GPER-1 agonist, G-1, show a reduction in endothelin-1 (ET-1)-mediated vasoconstriction, corresponding to a decrease in vascular tone (Brunsing and Prossnitz, 2011; Meyer et al., 2012; Revankar et al., 2005).

Recent evidence demonstrates the loss for tissue-specific E2 sensitivity with aging. For example, anti-inflammatory effects of E2 were lost following a 10 day period of hypoestrogenicity but not immediately following ovariectomy in animal models of stroke (Suzuki et al., 2007). Recent studies have confirmed these observations in middle-aged female rats and showed that a prolonged period of E2 deprivation leads to neuronal cell death and a specific loss of hippocampus CA1 ERα levels, while the uterotropic effects of ERα were preserved following global cerebral ischemia (Zhang et al., 2009). Moreover, it was demonstrated that the degradation of ERα via ubiquitination in neurons occurs as a result of a prolonged period of hypoestrogenicity in aged rats (Zhang et al., 2011), a mechanism which may help explain the critical period hypothesis. These studies demonstrate factors affecting complexities and efficacy of MHT on cerebral vascular parameters in postmenopausal women (see Section 2).

1.1.2. Signaling pathways of estrogen-induced vasoprotection

Similar to the peripheral circulation, E2 regulates cerebral vascular tone by modulating endothelial and smooth muscle cell functions, resulting in changes in vascular tone. As in peripheral endothelial cells, E2 facilitates the production of endothelium-derived release of vasoactive substances such as nitric oxide (NO), cyclooxygenase (COX) derivatives of arachidonic acid, the contractile agent ET-1 and endothelium-derived hyperpolarizing factor (EDHF) Duckles and Krause, 2007.

E2 decreases myogenic tone of the cerebrovasculature, indirectly, through NO-dependent vasorelaxation. NO has been extensively studied for its remarkable ability to signal the surrounding smooth muscle to relax by elevating cyclic guanosine monophosphate (cGMP) activity, thus increasing arterial blood flow (Pelligrino and Galea, 2001; Snyder and Bredt, 1992). Studies of female cerebral arteries demonstrate stronger NO-dependent vasodilation as compared to age-matched males or ovariectomized females (Geary et al., 2000). Additional evidence suggests that exogenous E2 supplementation in ovariectomized females promotes NO upregulation and cerebral arterial dilation, corresponding to a notable reduction in vascular tone (Geary et al., 1998; Weiner et al., 1994). One mechanism responsible for E2-induced NO-dependent vasodilation promotes an elevation in eNOS expression and activation. Prolonged E2 treatment increases eNOS production and enzymatic activity through an ER-dependent mechanism, as shown by using the selective ERα and ERβ inhibitor compound, ICI182,780 (McNeill et al., 2002). These effects are partially due to the activation of extracellular, pro-survival,