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Review

Estrogen: A master regulator of bioenergetic systems in the brain and body

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ABSTRACT

Estrogen is a fundamental regulator of the metabolic system of the female brain and body. Within the brain, estrogen regulates glucose transport, aerobic glycolysis, and mitochondrial function to generate ATP. In the body, estrogen protects against adiposity, insulin resistance, and type II diabetes, and regulates energy intake and expenditure. During menopause, decline in circulating estrogen is coincident with decline in brain bioenergetics and shift towards a metabolically compromised phenotype. Compensatory bioenergetic adaptations, or lack thereof, to estrogen loss could determine risk of late-onset Alzheimer's disease. Estrogen coordinates brain and body metabolism, such that peripheral metabolic state can indicate bioenergetic status of the brain. By generating biomarker profiles that encompass peripheral metabolic changes occurring with menopause, individual risk profiles for decreased brain bioenergetics and cognitive decline can be created. Biomarker profiles could identify women at risk while also serving as indicators of efficacy of hormone therapy or other preventative interventions.

1. Introduction

Estrogen is a systems-level signaling molecule that regulates and coordinates multiple functions across organs, cells and genes. To achieve this integration, estrogen utilizes a repertoire of receptors and signaling pathways to activate and regulate molecular and genomic responses required for survival at the cellular, organismic and ultimately whole body level. Estrogen integration and coordination of metabolism enables the development of peripheral biomarkers which can serve as reporters of brain bioenergetics, thereby providing early detection of populations at risk for neurodegenerative diseases associated with metabolic dysfunction, such as Alzheimer's disease. Reviewed herein is estrogen action in the brain and the body with particular emphasis on estrogen regulation of metabolism, and its clinical implications. Throughout, estrogen is used to refer to 17β-estradiol (the predominant estrogen) whereas other types of estrogens are specifically identified and typically are related to formulations of hormone therapies.

2. Estrogen, estrogen receptors, and intracellular signaling pathways in the brain

Estrogens are steroid hormones primarily known for their role in promotion of female sex characteristics and reproductive capability. There are three forms of estrogens in the female body: estrone (E_1), estradiol (E_2), and estriol (E_3). During a woman's reproductive years, the principal circulating estrogen is 17β-estradiol (E_2); importantly, it is also the most potent form of estrogen. In humans, estrogens are produced by the ovaries and adrenal glands, and circulate throughout the body where they have effects on most organ systems, including brain, breast, cardiovascular (heart and

Abbreviations: 3xTgAD, triple-transgenic mouse model of Alzheimer's disease; αERKO, ERα knockout; αKGDH, α-ketoglutarate dehydrogenase; Aβ, amyloid beta$_{1-42}$, beta-amyloid; AD, Alzheimer's disease; ArKO, aromatase knockout; BMI, body-mass index; CEE, conjugated equine estrogen; CMRglu, cerebral metabolic rate of glucose uptake; COX, complex IV; CSF, cerebrospinal fluid; DPN, diarylpropionitrile (an ERβ-selective agonist); E_1, estrone; E_2, estradiol, 17β-estradiol; E_3, estriol; Estrogen, 17b-estradiol unless otherwise specified; ER, estrogen receptor; ERα, estrogen receptor alpha, also referred to as ESR1; ERβ, estrogen receptor beta, also referred to as ESR2; ERE, estrogen response element; FDG, fluorodeoxyglucose; HOMA-IR, homeostatic assessment of insulin resistance; HT, hormone therapy; IDE, insulin degrading enzyme; IGF-1, insulin growth factor-1; IGF-1R, insulin growth factor-1 receptor; IR, insulin receptor; MCI, mild cognitive impairment; mER, membrane associated estrogen receptor; MMSE, mini-mental state exam; MPA, medroxyprogesterone acetate; mtDNA, mitochondrial DNA; OVX, ovariectomized, ovariectomy; OXPHOS, oxidative phosphorylation; PDH, pyruvate dehydrogenase; PET, positron emission tomography; PPT, propylpyrazoletriol (an ERα-selective agonist); rCBF, regional cerebral blood flow; ROS, reactive oxygen species; SHBG, sex hormone-binding globulin; T2DM, Type II diabetes mellitus; TCA, tricarboxylic citric acid; VaD, vascular dementia.

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vasculature), immune, reproductive (ovaries and uterus), bladder, skin, and bone (Kuiper et al., 1997).

Estrogen can cross the blood–brain barrier, and additionally, the brain can produce estrogen endogenously from cholesterol (Balthazart and Ball, 2006; Garcia-Ovejero et al., 2005; Prange-Kiel et al., 2003; Rune and Frotscher, 2005). Thus, along with its role in female physiology and reproduction, decades of research have established that estrogen is a critical signaling molecule within the brain (Brinton, 2008b). Estrogen receptors (ERs) are widely distributed in the brain, are present on both neurons and glia, and are expressed by both sexes. These receptors are highly evolutionarily conserved, with homologs in all vertebrate species. Estrogen receptors are composed of two general classes: nuclear ERs and membrane embedded/membrane associated ERs (mERs), both of which are present in the brain. There are two isoforms of classical nuclear estrogen receptors: ERα (ESR1) (HUGO Gene Nomenclature Committee, NCBI) and ERβ (ESR2) (HUGO Gene Nomenclature Committee, NCBI), which are functionally distinct and differentially distributed throughout the brain. Coding regions for both ERs are found on chromosome 6 (Menasce et al., 1993). The estrogen nuclear receptors exist initially as monomers, and dimerize prior to translocation to the nucleus, where they regulate transcription. *In vitro* evidence indicates the potential for heterodimers between ERα and ERβ (Pettersson et al., 1997), although *in vivo* evidence of this phenomenon remains to be established. In contrast to the nuclear receptors, membrane-associated estrogen receptors are monomers of ERα and ERβ. It is worth noting that in fish, a third nuclear ER has been identified, termed ERγ or ERβa (Halm et al., 2004; Hawkins and Thomas, 2004; Hawkins et al., 2000; Sabo-Attwood et al., 2004). The existence of this third ER in mammals has been investigated (Shughrue et al., 2002), and although no studies have provided concrete evidence for its presence, it would be presumptive to rule it out.

Classical estrogen signaling occurs as a result of the ER translocating to the nucleus, where it binds the estrogen response element (ERE) to regulate gene expression. Additionally, ERα can be alternatively spliced to generate three splice variants (GeneCards, ESR1), and ERβ can be alternatively spliced to generate eleven splice variants (GeneCards, ESR2). Most splice variants have been identified in breast or other cancer cell lines; because of the lack of genomic control in these cell lines, the functionality of splice variants is controversial. In brain, however, splice variants have been detected and have been associated with changes in estrogen responsivity.

2.1. Estrogen receptors alpha and beta: localization and splice variants

In rat and mouse forebrain, ERα shows a wide pattern of distribution (Brinton, 2009; Milner et al., 2001; Mitra et al., 2003; Shughrue, 2004; Shughrue et al., 1997); this is similar to the human brain, where *in situ* hybridization studies show ERα is distributed throughout the hypothalamus, forebrain, hippocampus (weakly), and amygdala (Mitra et al., 2003; Osterlund et al., 2000b; Ostlund et al., 2003). ERβ is more narrowly distributed, with high concentrations seen primarily in the hippocampus and cerebral cortex both in rodents and humans (Mitterling et al., 2010; Osterlund et al., 2000a; Ostlund et al., 2003; Shughrue et al., 1997; Shughrue and Merchenthaler, 2001). Within the hippocampus, both ERα and ERβ localize to dendritic spines, which are sites of synapse formation that show a high degree of plasticity. (Milner et al., 2005, 2001). ERα and ERβ have both been shown to mediate hippocampal-dependent learning tasks (Spencer et al., 2008); however, signaling through ERα and ERβ leads to differential expression of synaptic proteins, indicating that these two receptors have distinct roles within the hippocampus (Waters et al., 2009). In the rodent midbrain, ERβ is predominantly localized to the substantia nigra, locus coeruleus, and raphe nuclei (Mitra et al., 2003; Shughrue et al., 1997). ERα shows narrower distribution in the midbrain, and is primarily localized to the periaqueductal gray (Mitra et al., 2003; Shughrue et al., 1997). In the hindbrain and cerebellum, most ERα and ERβ immunostaining is within cell nuclei; the cerebellum shows no specific ERα staining, although it does show staining for ERβ (Mitra et al., 2003; Shughrue et al., 1997).

The effect of aging on ERα and ERβ expression and signaling is still a developing area of investigation, but a recent review thoroughly covers what is currently known (Foster, 2012). In short, data suggest that in different areas of the hippocampus, the ERα/ERβ ratio changes with age. In young and middle-aged rats, primates, and humans, ERβ is the dominant ER in the hippocampus, although ERα is present in low quantities. With aging, nuclear ERα localization increases in the dentate gyrus and CA3, but decreases in CA1 (Ishunina et al., 2007). ERα also becomes less sensitive to E_2 treatment as animals age; this is in contrast to ERβ, which shows decreased levels with age but remains responsive to E_2 treatment (Waters et al., 2011). Clinical studies have shown a linear relationship between Mini Mental State Exam (MMSE) score and ERα levels, but no relationship between MMSE and ERβ, in the frontal cortex of Alzheimer's patients (Kelly et al., 2008). The existence of variant isoforms of ERα that may influence cognitive impairment has been proposed (Kelly et al., 2008); this was later observed in a cohort of non-demented elderly (Yaffe et al., 2009). Thus the data show that decreased ERα levels and responsiveness may mediate cognitive impairment and dementia; during aging, although ERβ remains responsive to E_2, it is unable to compensate for the loss of ERα.

With aging, there is also an increase in the expression of particular ERα splice variants in the hippocampus that render much of the available ERα non-functional (Ishunina et al., 2007). Interestingly, it has been shown that elderly women are more likely than elderly men to have increased expression of ERα splice variants (Foster, 2012). ERβ splice variants are also present in the brain (Mott and Pak, 2012). A recent study proposed that one dominant negative splice variant, ERβ2, may mediate differential responses to E_2 treatment early and late after ovariectomy (OVX) in rats, such that only if estrogen treatment is initiated early after OVX is it able to prevent induction of the dominant negative ERβ2 variant (Wang et al., 2012). In addition to splice variants, there are several ERα polymorphisms that increase the risk of Alzheimer's disease (AD) specifically in women, particularly when associated with the APOE ε4 allele (Ryan et al., 2013).

2.2. Membrane-embedded estrogen receptors

In addition to the classical cytoplasmic and nuclear ERs, there are also membrane-embedded ERs, which rapidly initiate intracellular signaling pathways upon exposure to estrogen (Micevych and Dominguez, 2009; Toran-Allerand et al., 2002). These membrane sites of ER action activate both the Src/PI3K and Ras/Raf/MEKK/ERK signaling pathways, leading to activation of CREB, and they have been identified as required for E_2-inducible neuroprotection (Levin, 2001; Mannella and Brinton, 2006; Zhao et al., 2005). G protein-coupled receptors that associate with estrogen, such as G-protein coupled estrogen receptor 1 (GPER1; also called GPR30) (HUGO Gene Nomenclature Committee, NCBI), have also been identified (Maggiolini and Picard, 2010). This receptor has a high affinity for E_2, and signaling thorough it activates both cAMP/PKA and PI3K/Akt pathways (Maggiolini and Picard, 2010). 17β-estradiol binding to ERs activates signaling cascades associated with neuronal survival and function, including MAPK (Arevalo et al., 2012; Nilsen and Brinton, 2003; Singh et al., 2000), PI3K (Brinton, 2008a; Cheskis et al., 2008; Spencer-Segal et al., 2012), and PKC