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Review

Molecular signature of rapid estrogen regulation of synaptic connectivity and cognition

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ABSTRACT

There is now a growing appreciation that estrogen is capable of rapidly activating a number of signaling cascades within the central nervous system. In addition, there are an increasing number of studies reporting that 17β-estradiol, the major biologically active estrogen, can modulate cognition within a rapid time frame. Here we review recent studies that have begun to uncover the molecular and cellular framework which contributes to estrogens ability to rapidly modulate cognition. We first describe the mechanisms by which estrogen receptors (ERs) can couple to intracellular signaling cascades, either directly, or via the transactivation of other receptors. Subsequently, we review the evidence that estrogen can rapidly modulate both neuronal function and structure in the hippocampus and the cortex. Finally, we will discuss how estrogens may influence cognitive function through the modulation of neuronal structure, and the implications this may have on the treatment of a range of brain disorders.

1. Introduction

Steroid hormones, including estrogen, have long been known to influence nervous system development and function (Losel and Wehling, 2003; Bueno and Pfaff, 1976; Toran-Allerand, 1976). Estrogens are among the most studied steroid hormones and have consistently been shown to affect a broad range of physiological functions including reproductive, developmental, cardiovascular and neuronal function (Brinton, 2009; McEwen and Alves, 1999; Lee and Pfaff, 2008; Levin, 2011; Nilsson et al., 2001). One of the most studied effects of estrogen in the brain is its ability to enhance cognition (Brinton, 2009; McEwen and Alves, 1999; Craig and Murphy, 2007). While the enhancing effects of estrogen on cognition have consistently been reported in rodent and non-human primate model, evidence that estrogens are also capable of modulating cognition in humans have been more variable. Indeed, the findings of the 2003 Women's Health Initiative (WHI) study reported a decrease in cognitive function and an increased risk of dementia and stroke in women over 65 years of age who received conjugated equine estrogens plus medroxyprogesterone acetate (MPA) compared to those who received placebo (Espeland et al., 2004; Rossouw et al., 2002; Shumaker et al., 2004). However, it is now becoming apparent that the physiological status of women is critical in determining the effectiveness of estrogen on cognition (Asthana et al., 2009; Craig et al., 2005; Hogervorst and Bandelow, 2010; Maki, 2013; Maki and Henderson, 2012; Singh et al., 2013). Indeed, basic studies suggest that there is a critical period, or "window of opportunity" following menopause or surgical removal of ovaries, when the brain is still responsive to estrogens and the hormone can exert positive effects (Singh et al., 2013). Conversely, treatment with estrogens after this time may exert negative, or adverse, effects on cognition (Asthana et al., 2009; Maki, 2013; Sherwin, 2009). In addition, multiple studies in human females have reported that administration of estrogens have a positive effect on cognitive function, including memory (Hogervorst and Bandelow, 2010; Duff and Hampson, 2000; Hampson and Morley, 2013; Sherwin, 2012; Smith et al., 2006). Thus, understanding how estrogens influence cognitive function remains a highly active area of research.

Over recent years there has been a growing appreciation that the effects of estrogen in the brain can be mediated by the so-called "classic" long-term actions as well as rapid actions, which take place within minutes to hours. Rapid estrogenic actions have been shown to influence many different neuronal functions including synaptic plasticity, cognition, neuroprotection, hyperalgesia and homeostasis (Brinton, 2009; Woolley, 2007; Azcoitia et al., 2011; Srivastava et al., 2013). Recent evidence has also been presented suggesting that estrogens can be rapidly produced locally within discrete regions of the brain (Srivastava et al., 2013;

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Saldanha et al., 2011; Cornil et al., 2006; Azcoitia et al., 2011). The key enzyme, aromatase, required for the synthesis of 17β-estradiol (considered to be the major biologically active estrogen) has been reported to be expressed and regulated in an activity dependent manner, in a number of brain regions (Srivastava et al., 2013; Saldanha et al., 2011; Cornil et al., 2006; Azcoitia et al., 2011; Remage-Healey et al., 2011). Importantly, there is mounting evidence from rodent studies which illustrate that estrogen-induced rapid membrane-signaling can enhance cognitive processing, including memory processing and social behaviors (Luine and Frankfurt, 2012; Choleris et al., 2012).

In this review, we will highlight our current understanding of how estrogen can initiate rapid, membrane-signaling cascades relevant for both cognitive function and the remodeling of neural circuitry. In the first part, we will focus on the mechanisms by which estrogen receptors (ERs) can couple to intracellular signaling cascades, either directly, or via the transactivation of other receptors. We will then go on to explore the ability of estrogen to modulate both neuronal function and structure in the hippocampus and the cortex. Finally, we will discuss how estrogens may influence cognitive function through the modulation of neuronal structure, and the implications this may have on the treatment of a range of brain disorders.

2. Non-canonical estrogen signaling and cognition

Numerous studies using ER knockout animals and ER specific agonists/modulators have clearly demonstrated that estrogens have profound effects on a range of cognitive functions, including various memory processes and social behaviors (Brinton, 2009; Luine and Frankfurt, 2012; Choleris et al., 2012; Frick, 2009; Galea et al., 2008; Luine, 2008). The modulatory effects of estrogens on cognition have been described to occur within a rapid time scale (within hours) or over long periods (Luine and Frankfurt, 2012; Walf and Frye, 2008; Phan et al., 2011). Evidence has been presented for the involvement of the classical ERs, ERα and ERβ together with the newly identified G-protein coupled receptor (GPCR), G protein-coupled estrogen receptor 1 (GPER1) (also known as GPR30), in mediating these effects (Choleris et al., 2012; Walf and Frye, 2008; Ervin et al., 2013; Hawley et al., 2014). It should be noted that while GPER1 is reported to be an estrogen sensitive receptor, it seems that it has a much more complicated pharmacology and can be activated by multiple agonists (Evans et al., 2014; Srivastava and Evans, 2013). While the facilitation of cognition observed after long-term estrogen treatment are thought to result from gene transcription, mediated by classical nuclear actions of ERs (Frick, 2009; Aenlle and Foster, 2010; Foster, 2012; McDevitt et al., 2008), there is increasing evidence that the initiation of membrane-signaling pathways also play a critical role in estrogen-mediated enhancement of memory processing (Frick, 2009; Fernandez et al., 2008). Multiple kinase pathways including the extracellular signal-regulated kinase (ERK) pathway, the phospholipase C (PLC) pathway, Protein kinase C (PKC), phosphatidylinositol 3-kinase (PI3K)/Akt (also referred to as Protein kinase B; PKB) and Protein kinase A (PKA) pathways have been shown to be activated within minutes in response to 17β-estradiol treatment in neurons (Srivastava et al., 2013, 2011; Frick, 2009; Scott et al., 2012). Critically, several studies have implicated a number of these signaling pathways in 17β-estradiol-mediated enhancements of memory processing. For example, in ovariectomized young and middle-aged female mice, administration of 17β-estradiol rapidly causes the rapid activation of both ERK1/2 and PI3K/Akt signaling cascades, concurrent with an enhancement of performance in object recognition tasks (Fernandez et al., 2008; Fan et al., 2010). Importantly, inhibition of these kinases abolished 17β-estradiol-induced enhancement of object recognition (Fernandez et al., 2008; Fan et al., 2010) (Fig. 1). While such studies clearly indicate a critical involvement for specific signaling mechanisms in estrogenic enhancements of memory processing, there is considerable debate regarding the identity of the ER, or ERs, responsible for mediating rapid estrogenic membrane-initiated signaling. Moreover, it is unclear whether estrogen-mediated membrane-signaling is initiated by receptors integrated into or associated with the plasma membrane. Nevertheless, the mechanisms that allow these receptors to couple with signaling cascades are now becoming apparent.

2.1. Membrane initiated estrogen signaling

The ERs: ERα, ERβ and GPER1 are expressed throughout the central nervous system, although their relative expression levels and subcellular distribution vary across brain region and age (Brailoiu et al., 2007; Milner et al., 2005; Mitra et al., 2003; Mitterling et al., 2010; Waters et al., 2011). The ability of 17β-estradiol to activate different signaling pathways and modulate cellular events also varies across brain region and age (Srivastava et al., 2013); this in part may be driven by differential expression of ERs (Raz et al., 2008) but also points to divergent roles of ERs in different brain regions. Despite the canonical concept of ERs as transcription factors, it is now clear that ERα, ERβ and GPER1 can rapidly initiate membrane-signaling (Meitzen and Mermelstein, 2011; Micevych and Kelly, 2012; Srivatsava and Evans, 2013). It should, however, be noted that yet uncharacterized cell surface signaling molecules, such as ERX and the STX-sensitive Gq-membrane estrogen receptor (Gq-mER) may mediate some of the rapid signaling events initiated by 17β-estradiol (Micevych and Kelly, 2012; Toran-Allerand, 2004). This suggests that there are multiple estrogen-sensitive receptors that could account for the divergent signaling profiles seen in varying brain regions (Fig. 1). It has also been argued that the rapid effects of 17β-estradiol are mediated by different ER combinations in different neuronal cell types (Scott et al., 2012; Srivastava et al., 2011; Raz et al., 2008; Srivatsava and Evans, 2013; Spary et al., 2009; Akama et al., 2013). ERs have been localized to different subcellular compartments, including synapses, mitochondria, lysosomes and in membrane fractions (Milner et al., 2005; Mitra et al., 2003; Mitterling et al., 2010; Nishio et al., 2004). This diversity of subcellular localizations may further suggest that within a cell, different sub-populations of ERs are involved in activating distinct signaling mechanisms, resulting in specific cellular events. In addition, several studies have suggested that the rapid actions of estrogens may be mediated by splice variants of ERs (Toran-Allerand, 2004; Chung et al., 2007; Ishii et al., 2011; Ishunina and Swaab, 2008; Kobayashi et al., 2011; Wu et al., 2012; Zhao et al., 2005).

Studies using membrane impermeable estrogen compounds such as serum albumin (BSA)-conjugated or BSA-FITIC-conjugated 17β-estradiol, have provided considerable evidence that 17β-estradiol binds to the plasma membrane of neurons and can initiate signaling cascades. For example, in hippocampal neurons, BSA-FITIC-17β-estradiol has been shown to bind at extracellular sites, resulting in an elevation of intracellular Ca^{2+} levels and increased phosphorylation of ERK1/2 (Wu et al., 2011). In a similar manner, infusion of BSA-conjugated 17β-estradiol into the dorsal hippocampus of young ovariectomized mice has been shown to rapidly activate ERK1/2 signaling pathway and enhance object recognition memory (Fernandez et al., 2008). It has, however, been cautioned that the effects of conjugated forms of 17β-estradiol (either to BSA or horse-radish peroxidase (HRP)) could be occluded by unconjugated, or free, 17β-estradiol which may pass through the membrane and act on intracellular receptors (Stevis et al., 1999). However, the use of carefully filtered conjugated compounds,

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