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Review article

The role of estrogen receptor β and nicotinic cholinergic receptors in postpartum depression

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ABSTRACT

Postpartum depression (PPD) is a devastating disease occurring in approximately 20% of women. Women who suffer from PPD appear to be more sensitive to postpartum hormonal changes than women who do not experience this form of depression. Furthermore, women who quit smoking prior to or during pregnancy, and who develop PPD, are at an increased risk of smoking relapse. Unfortunately, the mechanistic relationship between the pathophysiology of PPD and smoking relapse is unknown. Here we review the roles of both estrogen receptor beta (ERβ) and cholinergic nicotinic receptors (nAChRs) in the pathogenesis of depression and propose a mechanistic rationale to explain the high rate of smoking relapse exhibited by women who develop PPD.

Contents

1. Introduction

Findings from the Centers for Disease Control and Prevention's Pregnancy Risk Assessment Monitoring System (PRAMS) suggest that estrogen-mediated effects on neuroendocrine function and interactions with the nicotinic cholinergic system may play a role in the pathogenesis of depression (Allen et al., 2009; Carmichael and Ahluwalia, 2000). This study monitored smoking behavior before, after, and during pregnancy and described relationships among hormonal fluctuations, nicotine exposure, and mood changes (Tong et al., 2009). Indeed, clinical studies have demonstrated that rates of depression increase when estrogen levels decline such as occurs during the postpartum period, following menopause, or in the context of treatment with the mixed estrogen receptor agonist/antagonist, tamoxifen, for hormone receptor sensitive breast cancer, times during which smoking relapse increases and cessation decreases (Arpels, 1996; McVay and Copeland, 2011; Steiner et al., 2003; Thompson et al., 1999).

Numerous studies have documented a role for neuronal nicotinic acetylcholine receptors (nAChRs) in depression (for reviews see Mineur and Picciotto, 2010; Picciotto et al., 2008) and an increased prevalence of smoking in depressed individuals (for review see Aubin et al., 2012). However, the relationship between nAChR activity and

Abbreviations: PPD, postpartum depression; ER, estrogen receptor; nAChR, nicotinic acetylcholine receptor; HPA, hypothalamic-pituitary-adrenal; CRH, corticotropin-releasing hormone; PVN, paraventricular nucleus; ACTH, adrenocorticotropic hormone; ERE, estrogen response element; GR, glucocorticoid receptor; ERK1/2, extracellular signal-regulated kinases; CREB, cAMP response element binding protein; OVX, ovariectomy; DEX, dexamethasone; KO, knockout; FST, forced swim test; αERKO, estrogen receptor α knockout; βERKO, estrogen receptor β knockout; αβERKO, estrogen receptor α and estrogen receptor β double knockout; WT, wild-type; DPN, diarylpropionitrile; PPT, propylpyrazoletriol.

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hormonal fluctuations has not been studied in depth. Although both estrogen-mediated neuroendocrine function and nAChRs have been implicated as playing a role in depression, possible crosstalk between these systems has not been well documented. Arguably the best known clinical manifestation of neuroendocrine disruption leading to depressed mood occurs in postpartum depression (PPD), a devastating disease that affects 10–22% of women and is often undiagnosed and untreated (Beck, 2001; Beck and Gable, 2001; Hobfoll et al., 1995; Kendler et al., 1993). Interestingly, epidemiologic associations between PPD and smoking support a relationship between ovarian hormone fluctuations and nicotine dependence. Women who suffer from PPD appear to be more sensitive to hormonal changes, and those individuals who quit smoking prior to pregnancy are at an increased risk of smoking relapse following delivery (Allen et al., 2009; Bloch et al., 2000; Carmichael and Ahluwalia, 2000; Tong et al., 2009).

This review summarizes our knowledge of: estrogen and depression, with a focus on the role of estrogen receptor (ER) β; the cholinergic system and depression, with an emphasis on the role of nAChRs; and interactions between these two systems in the pathogenesis and treatment of neuroendocrine-mediated depression, with an emphasis on PPD.

2. Estrogens and depression

Prior to adolescence, the rates of depression in girls and boys are similar (Born et al., 2002). With the onset of puberty, this ratio shifts, rendering women twice as likely to suffer from depressive disorders as men and suggesting that sex differences and circulating hormones predispose to this illness (Grigoriadis and Robinson, 2007). Furthermore, it is recognized that a subset of women are more vulnerable to depression and are prone to mood fluctuations during periods of hormonal change such as occurs surrounding menses, as well as during pregnancy, the postpartum period, and menopause (Graziottin and Serafini, 2009). Interestingly, women who experience symptoms at one of these times are more likely to experience symptoms during another, signifying that a fundamental physiologic alteration in hormonally-mediated processes may precipitate the development of mood disorders in these women.

Many studies attempting to link depression to hormonal changes have explored the role of estrogen in: promoting neuronal growth and survival in the hypothalamus, amygdala, hippocampus, and prefrontal cortex (Lee and McEwen, 2001); enhancing monoaminergic activity (Bethea et al., 2000; Gundlah et al., 1999; Osterlund et al., 2000); protecting against oxidative stress, glutamate excitotoxicity, and Alzheimer's pathology (Amantea et al., 2005; Pike et al., 2009); and regulating the hypothalamic-pituitary adrenal (HPA) axis (Cizza et al., 1997). Hormonal differences between men and women have a differential impact on the HPA axis and provide the basis for theories about sexual dimorphism in affective disorders (Flandreau et al., 2012; Goel and Bale, 2009; Hori et al., 2010; Shea et al., 2005). The activity of the HPA axis, which is increased in depression, is largely regulated by corticotropin-releasing hormone (CRH) released from the paraventricular nucleus (PVN) of the hypothalamus (Meltzer-Brody et al., 2011; Tsigos and Chrousos, 2002). In the central nervous system, CRH controls the synthesis of adrenocorticotropic hormone (ACTH) in the anterior pituitary gland (Fig. 1), which, along with other neuroendocrine hormones, mitigates the physiologic and neuropsychiatric effects of stress (Butler et al., 1990; Chappell et al., 1986; Melia and Duman, 1991; Swanson et al., 1983; Vamvakopoulos and Chrousos, 1993). Indeed, increased activity of CRH neurons in the PVN has been implicated in the pathogenesis of depression (Swaab, 2004).

The role of the HPA axis in PPD has been described in the context of the abrupt decline of ovarian hormones and their neuroactive steroid derivatives in the postpartum period (Groer and Morgan, 2007; Naert et al., 2007). In PPD patients, the relationship between ACTH and cortisol becomes dysregulated (Jolley et al., 2007), and correlations have

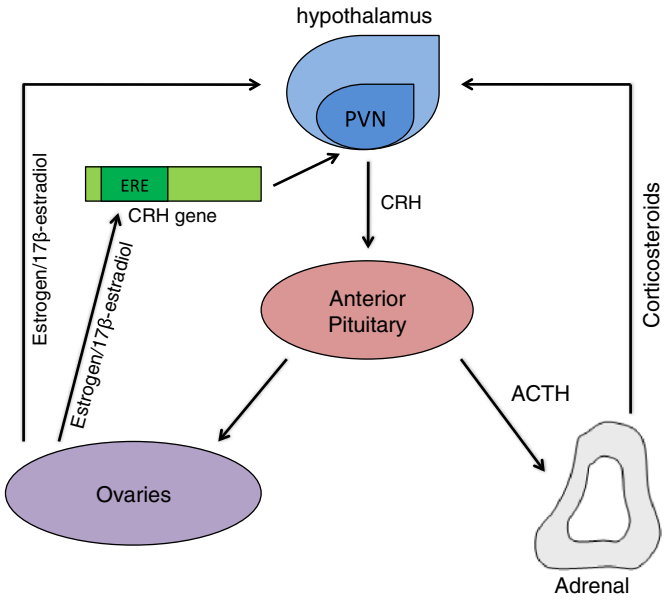

Fig. 1. Estrogen and the HPA axis. Evidence suggests that the HPA axis is the site of convergence for a multitude of genetic, epigenetic, and environmental effects. Estrogen/17β-estradiol regulates the HPA axis via: direct effects on the hypothalamus; modulation of CRH gene transcription by binding to estrogen response elements (EREs) in DNA; and modulation of glucocorticoid receptors (GRs) in the anterior pituitary, hypothalamus, and hippocampus in rats.

been demonstrated between HPA axis activity during pregnancy and the HPA axis response to postpartum stress (Meinlschmidt et al., 2010). Estrogen has an essential function in HPA axis regulation through: direct effects on the hypothalamus; modulation of estrogen response elements (EREs) within the CRH gene (Vamvakopoulos and Chrousos, 1993; Yang et al., 1996); and modulation of glucocorticoid receptors (GRs) in the anterior pituitary, hypothalamus, and hippocampus (Paulmyer-Lacroix et al., 1996; Sheng et al., 2003; Swaab et al., 2005). Indeed, the effects of estrogen on the hypothalamus were described more than 50 years ago when this brain region was shown to express high densities of ERs (McGrire and Lisk, 1969).

Two distinct ERs have been identified, ERα and ERβ. Signaling occurs via classical/genomic pathways in which ligand-bound ER dimers interact with EREs in target genes, or through non-classical pathways in which cell surface ERs are activated and alter transcription via the downstream effects of extracellular signal-regulated kinases (ERK1/2) and phosphorylated cAMP response element binding protein (CREB) (Bjornstrom and Sjoberg, 2005). Further, ERβ is capable of inhibiting the ligand-mediated transcriptional activity of ERα on the ERE-reporter gene (Ogawa et al., 1998) and inducing proteosome-dependent degradation of ERα through the formation of ERα/ERβ heterodimers in human breast cancer cells (Zhao et al., 2007).

ERβ plays an extensive role throughout the central nervous system. Increasingly, evidence suggests that the ability of estrogen to ameliorate mood symptoms in women is a function of activation of ERβ (Solomon and Herman, 2009). While the administration of selective ERα modulators have done little to quell mood symptoms in animal models, selective ERβ receptor agonists decrease depressive behaviors in mice post ovariectomy (OVX), and have anxiolytic properties in rats (Walf et al., 2009; Weiser et al., 2010). Although the expression of ERα and ERβ overlap in several brain regions, there are areas in which only one receptor is expressed, suggesting divergent functions. For example, ERα is expressed solely in the ventromedial hypothalamic nucleus, while ERβ is present largely in neurons of the PVN of the hypothalamus and tuberal hypothalamic nuclei, and is more abundant than ERα in the hippocampus (Hileman et al., 1999; Kuiper et al., 1997, 1998; Laflamme et al., 1998; Mitra et al., 2003; Weiser et al., 2008). ERβ immunoreactivity has been illustrated in