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Reviews

Estrogenic mediation of serotonergic and neurotrophic systems: Implications for female mood disorders

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ABSTRACT

Clinical research has demonstrated a significant sex difference in the occurrence of depressive disorders. Beginning at pubertal onset, women report a higher incidence of depression than men. Women are also vulnerable to the development of depressive disorders such as premenstrual dysphoric disorder, postpartum depression, and perimenopausal depression. These disorders are associated with reproductive stages involving changes in gonadal hormone levels. Specifically, female depression and female affective behaviors are influenced by estradiol levels. This review argues two major mechanisms by which estrogens influence depression and depressive-like behavior: through interactions with neurotrophic factors and through an influence on the serotonergic system. In particular, estradiol increases brain derived neurotrophic factor (BDNF) levels within the brain, and alters serotonergic expression in a receptor subtype-specific manner. We will take a regional approach, examining these effects of estrogens in the major brain areas implicated in depression. Finally, we will discuss the gaps in our current knowledge of the effects of estrogens on female depression, and the potential utility for estrogen receptor modulators in treatment for this disorder.

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1. Introduction

From puberty through menopause, women report higher rates of depression than age-matched men (Piccinelli and Wilkinson, 2000). Furthermore, differences in reproductive status contribute to antidepressant medication treatment response. Post-menopausal women self-report a decrease in efficacy of antidepressant drugs relative to pre-menopausal women (Pae et al., 2009). Growing literature suggests that the source of these sex and age-related differences in both depression epidemiology and treatment outcomes is linked to sex hormones. Women with depression show lower levels of estradiol during the follicular phase of their cycle (Holsen et al., 2011). An elegant study by Bloch et al. (2000) found that induced hypogonadism produced depressive symptoms in women previously

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diagnosed with postpartum depression, but not in control subjects. Subsequent treatment with estradiol and progesterone removed these symptoms (Bloch et al., 2000). Other studies have demonstrated a decrease in depressive symptoms following treatment with estradiol (Douma et al., 2005). Finally, incidence of depression in women runs parallel to reproductive stages associated with decreased estradiol production (Fig. 1). These stages include the premenstrual phase of the menstrual cycle, the postpartum period, and perimenopause (Douma et al., 2005).

Sex hormones have been linked to the efficacy of antidepressant drug treatment. Animal models have confirmed an enhanced effect of SSRI treatment following estradiol administration (Sell et al., 2008). In women, higher levels of follicular stimulating hormone predict a decreased effect of antidepressant medication (Pae et al., 2009). Furthermore, estradiol treatment combined with selective serotonin reuptake inhibitor (SSRI) treatment decreases the severity of depression symptoms in perimenopausal women more effectively than SSRI therapy alone (Westlund and Parry, 2003). In sum, estradiol alone and in combination with traditional antidepressant medications may alleviate depression symptoms in women experiencing major depressive disorder (MDD) or depressive disorders stemming from specific changes in gonadal hormonal milieu.

The present review seeks to summarize and critically assess the current literature on depression in females as mediated by estrogens. We will propose two main methods by which estrogens impact many of the major brain areas associated with depression- through alteration of neurotrophic and serotonergic systems. Additionally, we will focus on premenstrual dysphoric disorder (PMDD), postpartum depression, and perimenopausal depression, and describe current literature exploring the relationship between these disorders, estrogens, and known central nervous system sources of depression pathology. Finally, we will describe future directions for our field, emphasizing potential treatment options requiring further research.

2. Estrogens and the brain

The group of endogenous steroids termed “estrogens” is comprised of several hormones, including estrone, estradiol, and estriol. Of these, estriol shows the greatest increase in plasma levels during pregnancy, and estrone levels are higher during the menopausal transition (De Hertogh et al., 1975; Rannevik et al., 2008). Estradiol, the most potent of the estrogens, has been the best studied, and is the predominating estrogen during the reproductive period in females (Gruber et al., 2002). Additionally, estradiol has classically been the hormone of choice for steroidal replacement following ovariectomy in the preclinical literature. The major site of estrogenic production in females is the theca and granulose cells of the ovaries (McNatty et al., 1979). Estrogens enter the brain through the blood brain barrier, influencing neuronal activity by multiple pathways (Pardridge and Mietus, 1979). These hormones are highly lipophilic, allowing them to cross the cellular lipid bilayer and bind to intracellular estrogen receptors (ERs). Once bound, the estrogen–ER complex diffuses into the cell nucleus, binding to estrogen responsive elements, specific sequences of DNA, altering transcription. In the absence of estrogen responsive elements, ERs can affect transcription by binding to coactivators or repressors within DNA. ERs also impact gene activity by activating other transcription factors (Gruber et al., 2002).

ERs are widely distributed throughout the brain. Intracellular receptors ERα and ERβ show some overlap in both function and distribution, but are thought to differ in their roles in mediating affect (Weiser et al., 2008). ER receptor subtypes are located in many of the brain areas that are associated with depression (see Östlund et al., 2003), as we will discuss below.

Levels of estrogens fluctuate dramatically across the female lifespan (Fig. 1). Estradiol levels increase at menarche, then vary across each menstrual cycle, with levels peaking during the follicular phase, and decreasing during the luteal period (Abraham et al., 1972). During pregnancy, estradiol levels increase across each trimester, then steeply decline after parturition (De Hertogh et al., 1975). Finally, during the perimenopausal period, estradiol levels show an increase in oscillations due to shortened cycle length, followed by a gradual decline in levels during menopause (Sherman and Korenman, 1975). Changes in estradiol levels are correlated with region-specific changes in ER expression (Österlund et al., 1998). As we will report, differences in both estradiol and ER levels may contribute to depressive symptoms.

3. Major depressive disorder and reproductive mood disorders

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM) V, MDD is a common mood disorder with symptoms that include depressed mood, decreased interest in previously enjoyed activities, loss of energy, change in sleep patterns, inability to concentrate, and suicidal thoughts or ideations (American Psychiatric Association, 2013). One of the most robust findings in depression research is that the rate of MDD is much higher in women than in men, even after controlling for social and environmental factors such as help-seeking

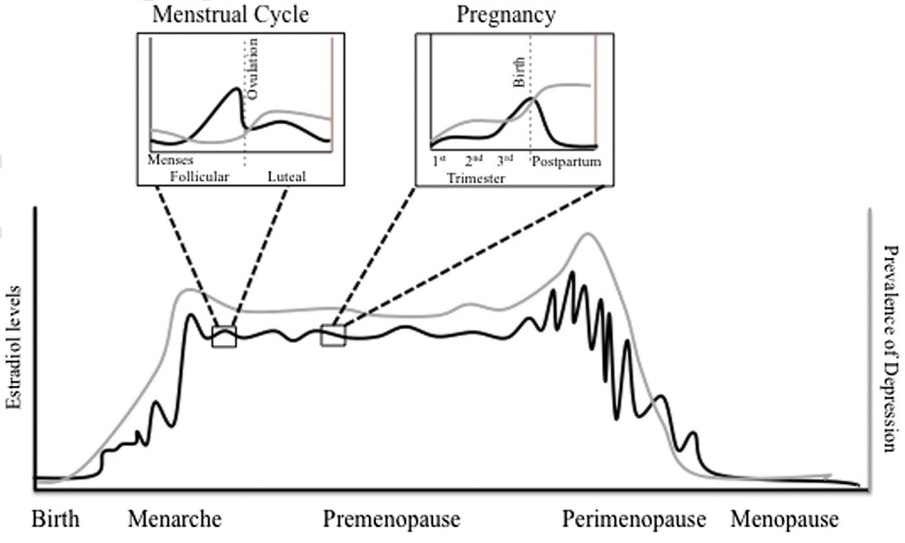

Fig. 1. Simplification of natural fluctuations in peripheral estrogen levels across the human female life span.

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