

Role of Interaction of Female Hormones with The Glutamatergic System in Neuropsychiatric Conditions

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Abstract

Hormones that are essential for reproductive function, fluctuations in hormone levels dynamically affect female brain morphology, function, neurochemistry and are likely to contribute to the risk of female-specific neuropsychiatric conditions such as depression and anxiety disorders. Ovarian hormones act on several types of receptors such as voltage-gated ion channels, including gamma-aminobutyric acid (GABA) N-methyl-D-aspartate (NMDA), serotonin and dopamine receptors. Glutamate acts as the main excitatory neurotransmitter in the central nervous system (CNS) and is a proximal regulator of cognitive domains such as learning and memory. The integration of glutamatergic transmission is fundamental to normal cognitive functioning and mental health. In this article, we present evidence that estrogen is not a simple risk or resilience factor for these disorders, but that its role is context-dependent, including age, reproductive status, and genetic makeup. In particular, we highlight the role of sex hormone fluctuations and estrogen imbalance in increasing women's vulnerability to neuropsychiatric disorders. Estrogens provide neuroprotective and anti-inflammatory effects. Estrogen and estrogen signaling are disrupted in multiple psychiatric disorders, with varying degrees of impairment affecting different parts of the brain. Future research elucidating estrogen and estrogen signaling disruptions and potential new treatment strategies for major psychiatric disorders and memory loss.

Keywords: estrogen; neuropsychiatric disorder; neurotransmitters; glutamate

Introduction

Over the past decades, several scientific fields have extended their understanding of the critical actions of ovarian hormones such as estrogen and progesterone beyond the reproductive tract. The brain is an important target for the actions of estrogen and progesterone, and both hormones mediate distinct neuroendocrine states by which brain structure and function are modulated throughout a woman's life. Both estrogen and progesterone act through classical genomic receptors as well as non-classical membrane-bound receptors [1]. Hormones that are essential for reproductive function, fluctuations in hormone levels dynamically influence female brain morphology, function [2], neurochemistry [3], and are likely to contribute to the risk of female-specific neuropsychiatric conditions such as depression and anxiety disorders [4]. In this article, we present evidence that estrogen is not a simple risk or resilience factor for these disorders, but that its role depends on context, including age, reproductive status, and genetic makeup. In particular, we highlight the role of sex hormone fluctuations and estrogen imbalance in increasing women's vulnerability to neuropsychiatric disorders. The ovarian hormones estrogen and progesterone have potent neuromodulatory effects and have been shown in a number of human and animal studies to shape female emotionality [5]. Estrogen has been shown to influence multiple

neurotransmitter systems in the brain, including the serotonergic, noradrenergic, GABAergic, dopaminergic, and glutamatergic systems, and thus may influence mood, emotion, and reward, as well as cognition and the relationship between other brain functions [3]. Classical estrogen receptors (ER α/β) [6] and progesterone receptors (PRA/B) [7] are highly expressed in brain regions involved in emotion and cognition, such as the amygdala and hippocampus. There is strong evidence that several limbic and cortical brain regions, including the hippocampus, amygdala, and prefrontal cortex (PFC), are involved in the regulation of anxiety- and depression-related emotions in mice as well as humans [8]. A review article by Dubol et al. summarized the results and assessed the level of evidence for 77 neuroimaging studies that examined the effects of the menstrual cycle on brain structure and function, involving a total of 1,304 women [9]. Sidney Yap et al compared glutamate levels in the medial prefrontal cortex of healthy perimenopausal (PM) women (n = 15) and healthy women with premenstrual syndrome (PMS) (n = 16) using magnetic resonance spectroscopy (MRS) with a 3 Tesla (T) magnet. The absence of depressive symptoms and psychiatric comorbidity was confirmed by a thorough interview and the participants were scanned during the early follicular phase (FP) of the menstrual cycle (MC). Thus, the results of the study suggest that changes in female hormones that occur

during PMS and PM may be responsible for the decrease in concentrations associated with glutamate levels [10]. Perimenopause is associated with decreased glucose levels in the medial prefrontal cortex (mPFC). This decrease may contribute to the increased risk of depression during the evening. Ovarian hormones can act on several types of receptors such as voltage-gated ion channels including GABA [11], NMDA [12], serotonin [13], and dopamine [14] receptors. Although estrogen and progesterone act on several areas of the brain, one area of the brain that has been the focus of many studies is the hippocampus, a brain region associated with various memory functions [15]. Ovarian hormones also have a profound effect on neurotrophins such as brain-derived neurotrophic factor (BDNF). BDNF has been shown to play a key role in neuronal survival, promoting neuronal regeneration after injury, and regulating the neurotransmitter system [16]. Estrogen treatment appears to increase BDNF expression in several brain areas including the hippocampus, amygdala, and cerebral cortex and reduces the risk of neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease. In addition to structural changes, ovarian hormone treatment is known to have significant effects on mood and cognitive function in areas such as working memory. Overall, both positive [17] and negative [18] effects on cognitive function have been reported during hormone replacement therapy (HRT). In view of these conflicting results, HRT is currently the subject of debate. However, it appears that timing and dose [19] are critical aspects of how the effects of HRT manifest. Throughout a woman's life, major hormonal transitions occur, beginning with rising estrogen levels at puberty, high estrogen levels during pregnancy and a rapid decline after childbirth, declining levels during perimenopause, and low levels in postmenopause. Interestingly, these major changes in sex hormone levels appear to be accompanied by increased incidence of mood disorders such as unipolar depression [20]. According to the monoamine hypothesis of depression, the depressive state is apparently accompanied by changes in the functioning and transmission of neurotransmitters. Ovarian hormones are known to have a modulating effect on synaptic transmission. These modulatory effects can be achieved by changing the reactivity of postsynaptic receptors [21] or presynaptic release of neurotransmitters [22]. The alternation of both mechanisms significantly affects the neurochemical systems involved in healthy emotional and cognitive control, such as the dopaminergic, serotonergic, glutamatergic and GABAergic (γ -aminobutyric acid) systems. Small changes in endogenous sex hormones that occur during the monthly cycle are also associated with mood changes [23]. As is known, the symptoms of the premenstrual period (PMS) include anxiety, irritability and depressive mood [24]. Glutamate acts as the major excitatory neurotransmitter in the CNS and is a proximal regulator of cognitive domains such as learning and memory [25]. The integration of glutamatergic transmission is fundamental for normal cognitive functioning and mental health [26]. Cortical glutamate projections are organized into descending and ascending pathways that project to most of the telencephalon. The effects of ovarian hormones on the glutamatergic system have been studied extensively, particularly in cell cultures and animal models [27]. In rodents, several mechanisms have been proposed by which ovarian hormones may influence glutamatergic neurotransmission: progesterone has been shown to suppress the excitatory glutamate response in a dose-dependent manner [28], while estrogen has a facilitatory effect on glutamate transmission [29]. In the results, several studies have demonstrated that physiological dose of progesterone in ovariectomized rats reduces glutamate response by 87% by attenuating non-NMDA receptors (AMPA, Kainate) [28], while the mechanisms underlying the effects of estrogen on cognitive function are associated with NMDA glutamate receptors. Estrogen has been shown to increase the expression of NMDA receptor subunits [30] and blockade of NMDA receptors with antagonists attenuates the effects of estrogen on neuronal correlates of memory. Moreover, estrogen facilitates the process of spinal maturation. Numerous animal studies have shown that estrogen with and without progesterone increases dendritic spines by activating the AMPA receptor [31] and NMDA receptors in the hippocampus and prefrontal cortex

(PFC). Estrogens can effectively protect neurons from glutamate-induced excitotoxicity [32]. Estradiol is the predominant estrogen in terms of activity and has thus been the focus of research. Estradiol can increase glutamate uptake by astrocytes (clearing it from the synaptic cleft), thereby helping to prevent excitotoxicity [33]. It is also thought to activate metabotropic glutamate receptor signaling via stimulation of estrogen receptors, demonstrating potential interactions at the receptor level [34]. Furthermore, ovariectomy reduces synaptic markers in these regions [35]. In addition to ovarian effects on spinal density, progesterone precursors such as pregnenolone have complex effects on glutamate release itself that depend on the developmental period of the brain region and functional status. In the hippocampus and prefrontal cortex [36], [37], which is important for memory and executive control, progesterone precursors have been shown to influence spontaneous glutamate release, which may promote synapse maturation or maintenance [38]. Direct interaction between ER α and metabotropic glutamate receptor 1a has also been observed in hormonally treated rats, providing further evidence for the activity of the estrogen receptor in hormonal and glutamatergic interactions [39]. Estradiol treatment can also increase the internalization of both metabotropic glutamate receptor 1 and ER α . These data are consistent with the current hypothesis of an estrogen receptor/glutamate receptor signaling unit, indicating the involvement of specific receptors in hormonal/glutamatergic interactions [40]. 17 β -estradiol (the major estrogen secreted by the ovaries in premenopause) promotes glutamate reuptake. Estradiol can also interact with metabotropic glutamate receptors, influencing neurological signaling activity [41].

Hormones that are crucial factors in reproductive function, fluctuations in hormone levels dynamically affect female brain morphology, function, neurochemistry and are likely to contribute to the risk of female-specific neuropsychiatric conditions such as depression and anxiety disorders. Estrogens and progesterone act on several types of receptors such as voltage-gated Na, Ca channels, including serotonin, dopamine, adrenergic, GABA and glutamate receptors. Glutamate acts as the main excitatory neurotransmitter in the central nervous system and is a proximal regulator of cognitive functions and emotional state. The integration of glutamatergic transmission is fundamental to normal cognitive functioning and mental health. We highlight the role of ovarian hormones fluctuations and estrogen imbalance in increasing women's vulnerability to neuropsychiatric disorders. Complex signaling cascades and receptor systems can be influenced by multiple physiological estrogens, as well as some physiological estrogens. Such influences could have profound effects on the functioning of the brain and nervous system. Future research elucidating estrogen and estrogen signaling disruptions and potential new treatment strategies for major psychiatric disorders and memory loss. These considerations should also inform future decisions about female sex hormone replacements, analogs, that alleviate life stage-specific effects of estrogens.

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