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Neurobiological Underpinnings of the Estrogen – Mood Relationship

Whitney Wharton, Ph.D.[1,2,3], **Carey E. Gleason, Ph.D.**[1,2,3], **Sandra R. M. S. Olson**[1,2,3], **Cynthia M. Carlsson, M.D., M.S.**[1,2,3], and **Sanjay Asthana, M.D., F.R.C.P. (C)**[1,2,3]

[1]University of Wisconsin, Alzheimer's Disease Research Center

[2]University of Wisconsin, School of Medicine and Public Health, Madison, Wisconsin

[3]Geriatric Research Education and Clinical Center, William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin

Abstract

Women are at a higher risk than men to develop mood disorders and depression. The increased risk is associated with fluctuating estrogen levels that occur during reproductive cycle events, particularly during the menopausal transition, a time characterized by drastic fluctuations in estrogen levels and increases in new onset and recurrent depression. Conversely, recent data show that hormone therapy, particularly transdermal estradiol formulations, may prevent mood disorders or even serve as a treatment regimen for women with diagnosed mood disturbances via estrogen regulation. While the exact mechanism is unknown, there is compelling scientific evidence indicating the neuromodulatory and neuroprotective effects of estrogen, which are directly relevant to mood symptomotology. Specifically, affective regulation has been linked to neural structures rich in estrogen receptors and estrogenic regulation of neurotransmitters. While a wealth of basic science, observational and clinical research support this rationale, potential mediating variables, such as estrogen formulation, proximity of administration to menopause, and the addition of progestins should be considered. Furthermore, the nature of postmenopausal exogenous hormone formulations in relation to premenopausal endogenous levels, as well as the ratio of estrone to estradiol warrant consideration.

Keywords

Estrogen Therapy; Hormone Therapy; Mood; Cognition; Affect; Women's Health Initiative

Introduction

This review will discuss the potential beneficial effects of estrogen on mood and affect in women, with an emphasis on exogenous estrogen administration during the menopausal transition. We open with a brief discussion highlighting the strong association between estrogen and mood. This includes a description of estrogenic hormones and the neuroendocrinology of estrogen levels across the lifespan, with particular attention to the menopausal transition. Next, we discuss the symptomotology of mood during periods of hormonal fluctuation. We then present the neurobiological underpinnings of estrogen's effects on mood, and explain how certain brain regions regulate affect via estrogen

Correspondence: Whitney Wharton, Ph.D., University of Wisconsin, School of Medicine and Public Health, William S. Middleton VA Hospital, 2500 Overlook Terrace, GRECC 11G, Madison WI 53705, wlwharto@medicine.wisc.edu, Phone: (608) 256-1901, ext. 11597.

receptors. Specifically, we will highlight neural structures including the amygdala, hippocampus and other non-mesial temporal regions that are involved in mood regulation and sensitive to estrogenic fluctuation. We conclude this section with a discussion of neurotransmitter regulation, focusing on the interactions between estrogen and the serotonergic system. In the final section, we examine the effects of estrogen administration on affective change. Estrogen formulations will be explored, as we highlight the fact that most basic science and recent clinical trials utilize estradiol as opposed to estrone formulations of hormone therapy (HT). We close with a discussion of the potential mediating factors that may influence the HT - mood relationship, followed by a review of ongoing clinical studies investigating HT in the treatment and prevention of negative affect, such as the Kronos Early Estrogen Prevention - Cognitive and Affective Study (KEEPS C/A).

Estrogen and Mood

Neurobiological Basis for Cognition-Enhancing and Mood Effects of Estrogen

The incidence of depressive disorders increases in both men and women after age 65 (1). These depressive disorders are usually chronic (2) and are associated with functional disability and decreased quality of life (3–5). The influence of sex hormones in the incidence of these depressive disorders has been well established (6, 7). Worldwide epidemiological studies report that the prevalence of major depressive disorder (MDD) among women is 1.5 to 3 times higher than in men (8). For women, data suggest that estrogen, or lack thereof, is strongly implicated in the regulation of mood and behavior, as well as in the pathobiology of mood disorders (9). These data are particularly important because the population continues to live longer, while the age of menopause remains unchanged. This extension of the lifespan means that many women will live almost half of their lives in a postmenopausal state, characterized by low estrogen levels that could possibly increase their risk for depression.

Research has consistently shown that women demonstrate an increased likelihood for new onset and recurrent depression during periods of marked hormonal fluctuation. Most notably, a number of studies have found an increased incidence of depression (10–12) and anxiety (13) in women across the menopausal transition, a period characterized by drastic fluctuations in estrogen levels before overall levels drop to approximately 10% of estrogen levels experienced premenopausally. While some studies have found that treatment with estrogen, and particularly estradiol (E2) alleviates depressive symptoms (14, 15), the mechanistic relationship between estrogen and depression remains unclear. While there is evidence to the contrary (16), a number of basic science, observational and clinical studies support a neurobiological basis for the multiple salutary effects of estrogen on mood during periods of estrogenic fluctuation, particularly as they pertain to the menopausal transition. If endogenous fluctuations in estrogen are responsible for negative affect, then it would follow that stabilizing estrogen levels via exogenous administration, such as hormone therapy (HT), would serve to regulate and improve affect. Indeed, some research demonstrates that HT can regulate and reduce depressive symptomotology (17).

Controversy in Hormone Therapy Research

Findings from the Women’s Health Initiative (18) (WHI) and its two ancillary studies, the WHI Memory Study (19) (WHIMS) and the WHI Study of Cognitive Aging (20) (WHISCA) have characterized the adverse effect profile and cognitive efficacy of conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA) in older postmenopausal women. The WHIMS found an increased risk for dementia in postmenopausal women aged 65 and older treated with CEE and MPA, the explanation of

which will be discussed later in this review. These results initiated much discussion regarding the possible limitations of HT treatment, prompting many users to cease HT administration. Subsequently, far fewer women considered HT to be a viable resource for the management of physiologic, cognitive and mood related menopausal symptoms. Here we present evidence that this general distrust by the public as well as by primary care physicians is misguided. Research advances prior and post WHI indicates the beneficial effects of some HT formulations, which have been overshadowed in the wake of WHI findings. Importantly, reports of the WHI findings were subsequently followed by a marked decrease in prescriptions of HT. Although interpretation remains open, one study demonstrated that the decrease in HT use was associated with a sharp increase in prescriptions of antidepressants to women over 40 years old (21, 22).

Two aspects of mood research warrant mention here. First, research has shown that positive and negative affect are independent dimensions and should be evaluated as such (23). It is arguably easier to identify and recruit participants with negative affect because these individuals are more likely to seek treatment and take medication. Furthermore, there are standardized methods and criteria to assess disorders of negative affect, such as MDD and post partum depression (PPD), as defined by the DSM-IV-TR. Thus, most research pertaining to mood relies on the presence or absence of a diagnosable mood disorder (24). Second, while mood and affect are often used interchangeably in the literature, there are distinctions between the two. As defined by the American Psychiatric Association (DSM-IV), mood refers to a sustained emotional state, while affect is used in terms of short-lived emotional changes. While we felt it necessary to elucidate this point, this review is unable to differentiate between mood and affect because of the definition flexibility in the majority of studies to date. We do however, make this distinction in hopes that future work follows suit, which will serve to increase scientific specificity and allow for more thorough reviews.

Neuroendocrinology of Menopause

Hormone therapy is comprised of different estrogenic formulations depending on the type of HT chosen by a woman and her physician. Estradiol (E2) and estrone (E1) are unique estrogen molecules, which bind to estrogen receptors (ER) differentially. E2 binds equally well to both types of ER (ERα and ERβ), while E1 binds preferentially to the ERα receptor. During her reproductive life, a woman's hormonal profile follows a predictable 28-day cycle. The cycle is characterized by a peak in E2 levels during the late follicular phase and a spike in the pituitary hormones (leutenizing hormone (LH) and follicle stimulating hormone (FSH)), during ovulation. This is followed by increasing levels of progesterone in the luteal phase. The rise in estrogen in the late follicular and luteal phases is primarily a result of increase in E2 and to some extent estrone (E1) levels. The hormonal milieu changes markedly with menopause and these changes have been well characterized (25). As a summary, Figure 1 (adapted from Gruber et al., (26) Michaud et al., (27) Romani et al. (28), and Hankinson et al. (29)) depicts estrogenic hormone levels associated with the different phases of the menstrual cycle and the postmenopausal state. E2 is the predominant circulating hormone prior to menopause. At menopause, however, E2 levels fall precipitously to approximately 10% of those found in menstruating women, while levels of E1 decline to a lesser extent (30). Also, both E1 and E2 continue to be synthesized by peripheral conversion of adrenal androstenedione and aromatization of testosterone (26), resulting in a shift in the E1/E2 ratio. Further, due to loss of feedback inhibition by low concentrations of E2 and other gonadal hormones, the levels of pituitary gonadotropins increase. Following menopause, the predominant form of estrogen in the body is E1; thus, for HT to mimic premenopausal physiology, it is necessary to administer E2. However, many clinical studies evaluating therapeutic efficacy of HT in healthy older women, particularly earlier work (i.e. the WHI), have utilized CEE, a preparation rich in E1.

The Effect of HT on Mood during the Menopausal Transition

There is evidence to suggest that women between the ages of menstruation onset and menopause are at increased risk for mood disorders (31, 32). A number of studies have found an increased incidence of depression (10–12) and anxiety (13, 33) in women undergoing the menopausal transition. Moreover, plasma E2 levels are significantly lower among depressed women (34), suggesting that low E2 may actually precipitate the incidence and/or symptomotology of mood disorders. In a very early study, Dalton (35) reported that of all women admitted to psychiatric hospitals, 46% were admitted during the menopausal transition. Furthermore, multiple studies have reported that women with a past history of depression (36, 37) or PMDD (38) and those undergoing surgical menopause (39, 40) may be at increased risk for mood disturbances during the perimenopausal period, compared to those without such histories.

It is generally believed that while several psychosocial factors such as changing life roles and attitudes about aging contribute to increased risk for mood disorders in perimenopausal women, (39, 40) the hormonal changes associated with the menopausal transition are primarily responsible for the increased risk of depressive disorders. Moreover, research shows that mood disturbances are not simply a result of additive menopausal symptoms, such as hot flashes and sleep disturbances. Evidence against the additive hypothesis has been illustrated in studies showing that E2 alleviates affective disorders in otherwise asymptomatic women, (i.e. women who report mood problems as their only symptom) (41). These data further support the view that hormonal regulation makes a significant contribution toward the pathobiology of depression and mood disorders. While it can prove difficult to directly relate hormonal changes to mood symptoms or disorders due to the extended period of the menopausal transition, evidence from clinical studies indicates that HT, particularly treatment with transdermal E2, successfully alleviates depressive disorders (42, 43).

Neurobiological Underpinnings of the Estrogen – Mood Relationship

Neurobiology of Estrogen

There is compelling scientific evidence indicating the neuromodulatory and neuroprotective effect of estrogen, which is directly relevant to mood symptomotology. Of note, the majority of basic science studies have employed E2 as opposed to E1, thus the neurobiology of estradiol has been characterized much more extensively than estrone. Here we present a review of the neurobiological and neuromodulatory actions of estrogen in order to examine potential mechanisms by which fluctuating estrogen levels may influence mood and affect, particularly across the menopausal transition.

Estrogenic Effect on Mood - the Amygdala

The amygdala, hippocampus and a number of non-mesial temporal structures are regions centrally involved in mood regulation, and have consistently demonstrated sensitivity to fluctuating levels of sex hormones such as estrogen (44). Of particular relevance to the present review is the amygdala, a neural substrate involved in the regulation of mood and memory. According to postmortem studies in humans, ER are most abundant in the amygdala, hippocampus and hypothalamus (45, 46). This is consistent with animal studies, which have reported that the amygdala has one of the highest densities of ER in the brain (46–49). The amygdala’s response to estrogen is multifaceted and is strongly linked to mood regulation. This relationship is observed with both endogenous and exogenous estrogen administration. For instance, dendritic spine density in the medial amygdala fluctuates across the estrous cycle of rats (50), and E2 administration increases the number of dendritic synapses in the amygdala (51). Recent work by Frey et al. found that rats exhibit a

statistically significant decrease in depressive behavior when E2 is injected subcutaneously into the amygdala (52). These data suggest that the amygdala is an E2-sensitive neural structure, which plays a role in the site-specific effect of estrogen on anxiety and depression.

Estrogenic Effect on Mood - the Hippocampus

Research has consistently shown that individuals with mood disturbances such as MDD have reduced hippocampal volume (for meta-analysis see Campbell et al. (53) and Videbech et al. (54)) and as a result, typical antidepressant treatments, such as SSRIs, increase neurogenesis in the hippocampus (reviewed by Duman et al. (55)). Similarly, estrogen exerts multiple beneficial actions on the hippocampus, which are directly related to mood symptomotology (56). A few of these actions include altering hippocampal plasticity, increasing dendritic spine density and increasing hippocampal volume and neurogenesis (57). This is consistent with data from animal models suggesting that estrogen exerts neurotrophic effects on mood, and these effects might be mediated by the hippocampus (58). Some research suggests that hippocampal changes due to depleting estrogen levels during the menopausal transition can be slowed or prevented with exogenous estrogen administration. For instance, two independent studies revealed that postmenopausal women using HT have larger hippocampal volume compared with non-users and men (59, 60). Maki et al. (61) also demonstrated that women using HT for at least two years had increased regional cerebral blood flow in the hippocampus, parahippocampal gyrus and middle temporal lobe when compared with non-users (61). Shafir et al found that women treated with HT had significantly greater activation in the right hippocampus and the entorhinal cortex compared to non-users, when processing negative images, as examined by fMRI. Also, our laboratory reported that longer exposure to HT regimens was associated with increased neuronal activation in the hippocampus, an area known to be affected in MDD (62).

Estrogenic Effect on Mood – Non Mesial-Temporal Regions

Mood is also regulated by brain regions unassociated with the mesial temporal lobe. Like the amygdalae and hippocampi, these regions express an abundance of ER. Of particular importance is the hypothalamus, a region known for its considerable estrogen-regulated plasticity and sensitivity to neuronal firing (63), and widely acknowledged action on mood regulation (for review see McEwen (64)). One study found that withdrawal of an eight week treatment of estrogen and progesterone induced depressive symptoms and disturbances of the hypothalamus in rats (65, 66). Also, attenuation of serotonin receptor signaling (discussed in detail later in this review) in the hypothalamus is considered important for the therapeutic effectiveness of SSRIs in the treatment of depression (67). In addition to the hypothalamus, studies have also shown significant estrogenic effects in the basal forebrain (medial septum), the diagonal band of Broca, and the nucleus basalis magnocellularis (NBM) (66). Like the hypothalamus, research shows that these regions express ERα and ERβ (68, 69), indicating that they are receptive to regulation by estrogen (70).

Taken together, these results lend support to the hypothesis that estrogen plays a significant role in mediating mood and affect via site-specific neural structures, the primary regions being the amygdala, hippocampus and the hypothalamus. Namely, women who use HT during the menopausal transition are more likely to show enhanced neuronal modulation and activation, particularly in areas selective to mood regulation. These data suggest that HT may be protective against structural changes associated with the menopausal transition and could prove to be an effective treatment strategy in women diagnosed with MDD.

Estrogen Augments the Function of Multiple Neurotransmitter Systems

There is cumulative scientific evidence supporting the facilitative role of estrogen on various neurotransmitter systems involved in the regulation of mood and affect (See van Amelsvoort et al. (71) and Yaffe (72) for reviews). Among others, the neurotransmitter systems directly up-regulated by estrogen include serotonin, acetylcholine, and the catecholamines (i.e., dopamine, epinephrine, and norepinephrine), all of which have been implicated in the modulation of mood processes. Of particular relevance to mood is the serotoninergic system (5–HT) (73) (74–77). Indeed, a number of recent studies have suggested that factors which primarily increase serotonergic and noradrenergic transmission are also efficacious in the treatment depression in peri- and postmenopausal women (78–80)

Serotonergic System

Interactions between estrogen and serotonin have long been acknowledged with regard to reproductive behaviors in animals (81). More recently, research suggests that estrogen and serotonin likely interact with regard to mood and affect in both animals and in humans, and could serve as a compounding mechanism by which estrogen influences emotion. Estrogen increases serotonergic postsynaptic responsivity (82), increases the number of serotonergic receptors, and enhances serotonergic transport and uptake (83, 84). Estrogen also facilitates synthesis of serotonin and the levels of its metabolite, 5-hydroxyindoleacetic acid (5–HIAA) (85). Furthermore, estrogen upregulates serotonin 5-HT1 receptors and downregulates 5-HT2 receptors, and decreases monoamine oxidase (MAO) activity (86) Thus, estrogen is a serotonergic agonist that responds via multiple mechanisms in brain regions implicated in mood regulation (9).

Serotonin generating neuronal cell bodies are located in the raphe nuclei of the midbrain and have projections throughout the hippocampus and the amygdala, brain regions discussed above, which are linked to both estrogen and mood. Similarly, serotonin receptors including the 5-HT1A, 5-HT2B, 5-HT2C, 5-HT3, and 5-HT4 are present through pathways in limbic structures such as the amygdala, cingulate gyrus, and hippocampus (87) and are directly associated with emotion regulation. For instance, one study reported that anxiety symptoms increased in ERβ knockout mice, along with increased amygdala response and 5-HT1A receptor expression (88). Such evidence supports ER involvement in serotonin regulation and maintains estrogen's importance in emotional processing.

In addition to serotoninergic mechanisms, estrogen up-regulates the activities of several other neurotransmitter systems important for regulation of mood, including the dopaminergic (89–92), and catecholaminergic (93–96) systems. Estrogen also appears to favorably modify the activities of both the nicotinic and muscarinic receptors (97, 98). In sum, estrogen appears to have complex and differential effects on neurotransmitters. Furthermore, there is increasing evidence that estrogen simultaneously acts on neurotransmitters and the neural substrate discussed above, suggesting that there could be an interaction between neurotransmission and specific brain structures (73, 99).

Effect of Estrogen Administration on Affective Change

Basic Science Overview

Basic science supports the role of estrogen in both the prevention and treatment of mood disorders associated with the menopausal transition. Most recently, Frye et al. (58, 100) reported that ovarectomized female rats treated with E2 exhibited improved cognitive performance and reduced anxiety and depressed behavior. Similarly, withdrawal from chronically sustained E2 levels in recently ovarectomized rats increases depressive behavior (101). Basic research has also produced persuasive evidence in support of the potential

antidepressant effect of E2 (63). As discussed earlier, estrogen increases serotonin postsynaptic responsivity and number of receptors, as well as serotonin uptake and synthesis, all mechanisms which have direct implications on mood regulation.

Studies in Non-Depressed Women

Observational studies suggest that HT is associated with improved cognitive function, mood, and quality of life (102) and decreased risk of depressive symptoms (103, 104). A number of longitudinal studies have been directed at assessing mood fluctuations and depression across the menopausal transition in non-depressed women (36, 105–110). All but one of these studies (109) support the notion that women are at increased risk for depression and mood disorders during menopause (111). In one study, 11 of 29 asymptomatic, regularly cycling, premenopausal women developed new-onset depression during the menopausal transition, as determined by subjective mood rating scores (110). Furthermore, the majority (nine) of depressive diagnoses in these women occurred during perimenopause, which is characterized by drastic fluctuations in estrogen levels. These data suggest that incidence of depression among women who have never been diagnosed with a mood disorder may be increased during the menopausal transition.

Clinical Studies Utilizing Estrogen for the Treatment of Depression

Over twenty placebo-controlled clinical studies have utilized HT as a treatment for peri- and postmenopausal women diagnosed with depression. Early research in this area suggested that HT was not a sufficient treatment for depression unless administered in very high doses (112). Though some trials continue to report that HT does not produce an antidepressant effect (42, 113), many studies have shown that perimenopausal women with depression respond well to treatment with E2 (15, 41). For instance, two recent double-blind, randomized placebo-controlled studies (15, 41) found that transdermal E2 alleviated depression in perimenopausal women. In one study, transdermal E2 alleviated depression in 68% of women, compared to only 20% of women in the placebo group (15). Moreover, the antidepressant effect remained significant after a 4-week washout period. Importantly, clinical studies that did not report a salutary effect of HT on mood symptoms mainly utilized mainly E1 formulations (114–116) and a subset of the studies included women who were concurrently taking psychotropic medication for psychiatric illness (115, 116).

Potential Mediating Variables in Estrogen / Mood Research

Many of the discrepant findings in mood - estrogen research can be partially explained by between-study heterogeneity in methodological, diagnostic, population, and design based differences. Also, much headway has been made in the HT research realm, which has almost certainly influenced study efficacy and mood symtomotology to a great degree. While there has been tremendous headway, several variables that might clarify the conflicting findings regarding estrogen remain largely unexplored. In particular, the differential effects of various hormone preparations and doses, as well as the effect of concomitant progestin therapy, hysterectomy status, prior history of HT exposure, prior mood diagnoses, and the influence of additional menopausal symptoms such as hot flashes and decreased sexual functioning should be taken into account. Here we discuss three of the most widely investigated variables hypothesized to mediate the estrogen – affect relationship.

Formulation and Route of Estrogen Administration

Differences in the pharmacokinetic aspects of oral versus transdermal and vaginal estrogens may contribute to the lack of consistency in clinical studies investigating the influence of HT on mood (117). Oral preparations are subject to extensive hepatic metabolism, which increases the risk of venous thromboembolic complications by inducing pro-coagulant

proteins. Unlike oral preparations, transdermal estrogen preparations do not increase binding glycoproteins, such as sex hormone binding globulin (SHBG), which results in higher plasma concentrations of free E2. The result is a more stable, beneficial effect on mood compared with oral estrogens.

Oral estrogen is mainly comprised of E1, while transdermal formulations utilize E2. Research shows that the superiority of E2 to E1 can be attributed to the overall estrogenic stability exerted by E2 (discussed below) as well as the ratio of circulating estrone to estradiol that is ultimately obtained. Oral E1 formulations result in an E1 : E2 ratio of approximately 5 : 1 to 7 : 1 (118). In contrast, transdermal E2 administration bypasses hepatic metabolism and results in a steady-state concentration of estradiol with an estrone : estradiol ratio of 1:1, approximating levels seen prior to menopause. Multiple clinical studies have reported the salutary effects of transdermal E2 on mood, while trials that failed to detect a positive impact on mood mainly utilized oral CEE preparations (118). Research examining E2 has resulted in alleviation of negative affect in studies investigating PPD, (119) premenstrual syndrome (PMS) (120) and perimenopausal depression (14, 15) Additionally, a recent review reported that current data supports the use of transdermal E2 in the management of depression in the context of menopausal transition (111).

Critical period hypothesis

One aspect of HT administration that may influence efficacy is the duration of time that elapses between natural menopause or hysterectomy, and the time that HT is first initiated. It appears that HT's beneficial effects on mood and cognition are prevalent in younger postmenopausal women, but less so in women who are five to ten years postmenopaual (121). Indeed in older women, HT has not been shown to benefit mood (122). There is converging evidence from clinical, observational and basic science research (58, 118, 123), that the potential beneficial effects of HT on cognition and mood are likely to be observed if HT is initiated during the perimenopausal period – a theory known as the "critical period" hypothesis.

The Effect of Progesterone on Mood

Progestins are prescribed in combination with estrogen (opposed HT) to prevent endometrial cancer in non-hysterectomized women. The relationship between progestins and mood in humans is not clearly understood. Some research has failed to find an association (41, 42), others have linked opposed HT with only small increases in depressive symptoms (124, 125), while one report stated that "it is mainly the addition of progestogen that seems to provoke these negative mood symptoms (126)." However, the same study reported that a high doses of MPA reduced negative mood symptoms and enhanced positive mood symptoms in women with prior PMS (126). Not only is the presence of progestins likely influential, but research shows that mood can also be attributed to differential progestin preparations. For instance, synthetic progestins (such as MPA), as opposed to natural progesterone, have been implicated in mood disturbances (127); however, MPA alone does not appear to produce dysphoric effects in postmenopausal women (128), and one large study failed to show an association between opposed HT therapy and depressive symptoms (104). While the relationship between mood and HT is not markedly defined, the presence and type of progestational administration should be noted, due to its mediating potential.

Fluctuating Estrogen Levels vs. Absolute Levels

We have reviewed evidence that reproductive events associated with changing the premenopausal hormonal milieu, such as certain phases of the menstrual cycle, the post-partum period and the menopausal transition are associated with depression in women (81). The adverse mood symptomotology that occurs during these reproductive events are

comparable and have been thoroughly described in the literature (129). Not only are these hormone-related events exhibited similarly, but they also share a congruous physiological profile characterized by drastic fluctuations in estrogen levels.

Depressive disorders and related symptomotology likely occur due to excessive hormonal fluctuations or an underlying vulnerability to these variations, rather than to absolute low levels of sex steroids. During reproductive events, most women exhibit estrogen levels within normal limits, yet report adverse mood symptoms. In fact, no study has identified consistent differences in plasma levels of reproductive or adrenal hormones in women with perimenopausal depression (121). Evidence against the low estrogen level hypothesis can be found throughout the estrogen / mood literature. For instance, chronic administration of E2 to ovariectomized rats and mice at doses much higher levels than natural physiological E2 levels, increases anxiety and depressive behaviors (130, 131). While we do know that chronically low levels of estrogen contribute to increased risk of atherosclerosis and cognitive impairment, the mood disturbances discussed throughout this review likely arise due to estrogenic fluctuations. We postulate that these reports are either a result of 1) women's differential sensitivity to normal steroid levels, such that excessively sensitive women (particularly women with a history of PPD) are destabilized by normal changes in estrogen levels (132) or 2) though estrogen levels remain within 'normal' limits, drastic fluctuations lead to inadequate regulation of mood (perhaps via irregular neural activation and / or neurotransmitter regulation discussed previously) (133).

While research investigating women with a history of mood disorders is supported by the differential sensitivity theory, the majority of women (i.e. those without a diagnosed mood disorder such as PPD) are also at increased risk of mood disorders and likely exhibit adverse mood symptomotology because of drastic estrogen fluctuations (133, 134). Several basic science, observational and clinical reports support this model (106, 108). In rats, depressive-like behavior varies as a function of the estrous cycle, decrease during pregnancy, and increase upon estrogen withdrawal (See Solomon et al. for a concise Review) (133). In women, observational research suggests that monophasic oral contraceptives stabilize mood across the 28-day cycle via regulation of estrogenic and progestational levels. The same can be said about HT. Exogenous estrogen administration not only increases overall levels of estrogen, but also serves to regulate hormone levels by preventing fluctuations.

Estrogen Fluctuations and the Estrone to Estradiol Ratio

Fluctuating estrogen levels may also result in irregular concentrations of E1 to E2, a factor that is indicative of overall estrogenic stability and heavily influenced by the presence and formulation of HT administration. Unlike oral HT formulations, transdermal E2 provides minimal fluctuation of plasma estrogen levels and result in overall estrogen levels comparable to the premenopausal physiological estrone : estradiol ratio. As mentioned earlier in this review, E2 binds equally well to both types of ER (ERα and ERβ), while E1 binds preferentially to the ERα receptor. Thus a treatment that binds to both ERs (E2) could arguably sustain the premenopausal E1 to E2 ratio if administered to healthy women during the premenopausal transition. The fact that the majority of clinical studies utilizing E2 formulations result in beneficial mood effects suggests that a regimen which provides more stable levels of estrogen (via E1 : E2 ratio) could optimally benefit women during a periods of marked hormonal instability, such as perimenopause (9). This steady-state administration of hormones may also result in stabilization of functional neurotransmitters such as serotonin and acetylcholine, which were discussed earlier in this review (135, 136).

Future Directions in Research

One of the most certain yet misunderstood characteristics of female biology is the influence of fluctuating sex hormones on mood. Hormonal variations begin with menstruation and continue past a woman's reproductive life. Variations are amplified during pregnancy and followed by an abrupt postpartum withdrawal, and for some women, end with the administration of HT. Considering the interactions between estrogen receptors, neurotransmitters and mood, this inherent repeated instability likely plays a role in the vulnerability to affective disorders in women, particularly as a function of increasing age (9, 117). Taken together, the majority of data support the hypothesis that transdermal E2 formulations of HT have beneficial effects on mood, and could be a viable treatment option for women with and without prior mood disturbances, and may also serve as a treatment for women with depression.

While many recent advances in HT and mood research have been made, large, long-term randomized clinical trials examining the effect of HT on mood are necessary to clarify the many remaining mechanistic questions (111) outlined in this review. The KEEPS Cognitive and Affective (C/A) Study is the first multisite, randomized, placebo-controlled, double-blind, parallel-group design clinical study that will address the major HT and mood related issues. Specifically, the C/A Study will evaluate the differential efficacy of CEE and transdermal E2 on comprehensive measures of mood in perimenopausal women over an extended therapy of four years. In conclusion, we believe that the KEEPS C/A study will provide much needed answers regarding the use of estrogen during the menopause and postmenopausal periods for the prevention of mood disorders.

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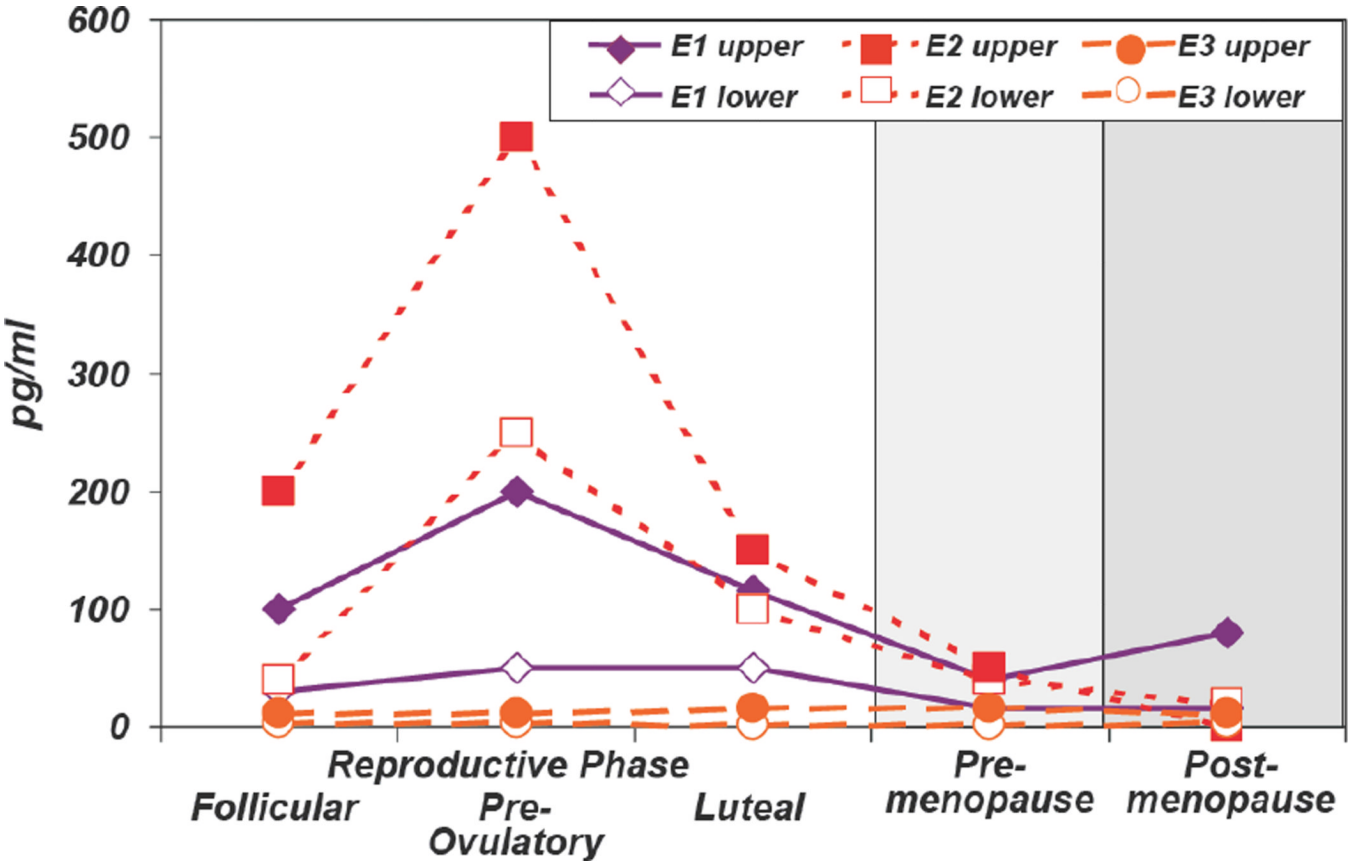

Figure 1.
Endogenous Estrogen Levels