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Cognitive Impairments of Major Depressive Disorder: Hippocampal Involvement and Modulation by Estrogen Receptor β (Erβ) and Acetylcholine

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Abstract

The pathology of major depressive disorder (MDD) involves many physiological systems, including the estrogen system, the acetylcholine system and the hypothalamus-pituitary-adrenal axis (HPA-axis). This review explores the influence of these three systems on mood and memory with emphasis on involvement of the hippocampus. Behavioral and physiological symptoms of MDD, including cognitive and mood impairments, can be mitigated or exacerbated by estrogenic activity, as well as by modulations of the acetylcholine system. In addition, HPA-axis dysregulation is thought to contribute to the hippocampus-mediated cognitive impairments characteristic of MDD. Particularly, we focus on the role of selective estrogen receptors in HPA-axis function that affect hippocampal modulation of mood and memory. Increased estrogenic activity in the hippocampus is correlated with enhanced memory and mood, and increased estrogen receptor ß activity has been shown to enhance mood and hippocampus-dependent memory independent of other estrogen receptors. Furthermore, we present evidence to support the utility of pharmacological agents that target estrogen receptor ß for mood and memory enhancement for the treatment of MDD.

Keywords: MDD, ERβ, Acetylcholine, HPA-axis, Hippocampus, Memory impairment

Introduction

Major Depressive Disorder (MDD) is an affective disorder characterized by a combination of symptoms that prevent a person from functioning normally, including persistent sadness, guilt, irritability, loss of interest in activities once pleasurable, fatigue, cognitive and memory impairment, changes in appetite, and discomfort or pain that do not ease with treatment.[1] MDD patients also display hypothalamic-pituitary-adrenal (HPA) axis dysfunction and elevated basal cortisol and low serum brain-derived neurotrophic factor (BDNF).[2-4] Untreated MDD leads to cognitive defects

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including retrograde amnesia and memory acquisition impairment,[5-7] which can be partially improved with antidepressant treatment.[6-10] Brain tissue blocks taken from deceased, unmedicated MDD patients show total glial cell reduction, decreased glial density,[11,12] and neuronal atrophy.[11] Depressive-like behaviors are correlated with glial and neurodegeneration in rats[11] and antidepressant treatment of depressive-like behavior has been shown to initiate neurogenesis in animal models.[13,14] MDD patients often show a volumetric reduction in certain brain areas, including the prefrontal cortex (PFC), amygdala, and hippocampus (HIP)[15-19] with the percent reduction in volume being correlated to either early-life trauma or time spent depressed.[15,19]The HIP is a brain structure involved in regulating mood[14,1518,20-22] that has been shown to mediate contextual and temporal spatial recognition memory (object location memory) in rats[23-25] and mice.[26] Effective antidepressant treatments are correlated with neuroproliferation in animal models[14,16,27] and human HIP culture, and have been shown to stop or reverse MDD-related HIP volumetric reduction.[15]

Serum BDNF is reduced in MDD patients,[3,4,16,28] corresponding to reduced neuronal plasticity, neuroproliferation, and cell survivability,[11,16] which may account for the volumetric reductions in brain structures such as the HIP that are seen in MDD patients.[14,15,18,20,29] Antidepressants, as well as non-pharmacotherapeutic antidepressant treatments such as exercise[2] and electroconvulsive therapy,[14] increase HIP neuroproliferation and neurogenesis[11,14,16] but HIP neurogenesis alone is not sufficient to relieve depression,[14] suggesting that neurodegeneration is a symptom, and not the underlying cause, of MDD. In fact, glial cell death is largely responsible for MMD-associated volumetric reductions in the CNS,[11,12] and glial loss rather than neuronal loss, in the prefrontal cortex (PFC) has been shown to induce depressive-like behaviors in rats.[11] The neuroglial atrophy affects oligodendrocytes,[12,15] which have a primary role in myelination and may be reduced due to elevated glucocorticoid secretion from HPA axis dysfunction.[15]

Approximately 17% of Americans experience at least one major depressive episode during their lifetime,[30] and women are twice as likely as men to suffer from MDD and other forms of unipolar depression.[30-32] The higher incidence of depression begins at puberty and lowers after menopause,[32,33] and depressed women have significantly lower levels of free estrogen (E_2) than non-depressed counterparts. Additionally, women with history of depression exhibit reduced fertility, menstrual abnormalities, and early menopause,[34,35] suggesting a role for female sex hormones in the etiology of depression.

Hippocampus

There is evidence that the ventral HIP mediates emotional regulation,[36-38] which may contribute to the pathology of mood disorders. While the regulatory mechanism is not yet defined, postmortem analysis[15] as well as visualization with PET and fMRI scans[18,19] have found volumetric reductions in the HIP of MDD patients that correlate with severity of depression[15] or length of time spent depressed.[18]

Further evidence for HIP involvement in MDD is found in MDD's correlation with impairments in memory acquisition,[39] specifically visuospatial learning[7] and verbal and visual recognition memory.[39,40] The HIP and parahippocampal brain regions have been implicated in mediating recognition memory, including object, location, and context recognition.[24,41-44] Impaired object discrimination is correlated with HIP damage,[23,41-44] and other brain regions, specifically the perirhinal cortex in rats.[41,42,45] Damage to the HIP has been shown to impair object location recognition in rats[23,24,43], and disconnection of HIP-perirhinal as well as HIP-medial prefrontal cortex have been shown to impair object location and temporal recognition in rats.[23] The relationship between HIP atrophy, memory impairment, and mood alterations suggests common etiology and that evaluation of HIP function could potentially measure the severity of depression, as well as the efficacy of

antidepressant treatments.

Both septal and splenial parts of the dorsal HIP, including CA1 neurons, are required for spatial learning[36-38] and memory recall.[36] The CA1 region is involved in temporal pattern association and memory formation, while the CA3 supports spatial pattern association and memory formation,[46] and is required for recognizing spatial novelty, along with the dentate gyrus (DG) and the perirhinal cortex. The first step in the formation of episodic memory begins with the DG routing information from the entorhinal cortex (EC) and then to the CA3[38,47] to consolidate spatial pattern separation. The CA3 region then feeds to CA1, which, due to the high ratio of CA1 to CA3 neurons, amplifies and outputs to the neocortex via the subiculum.[48] Therefore, the selective types of memory impairment in MDD may indicate damage in discrete hippocampal regions, notably the DG and CA3 regions.

Chronic Stress

Stressful events, especially during early life, increase the risk of developing MDD in adulthood,[14,17,21,48],and there is evidence that depressed women with a history of child sexual abuse or neglect display reduced HIP volume[20,29] and memory impairment.[4,20] Early life chronic stress models of depression, such as neonatal maternal separation, manipulate the physiological and behavioral characteristics of the adult animal by inducing stress response during periods of rapid development.[16] Rats exposed to early life stress display a suite of behavioral and physiological changes that persist into adulthood including depressive-like behaviors,[17,21] anxiety-like behaviors,[17,50] elevated basal corticosterone (CORT)[21,50] reduced serum BDNF,[28] and reduced HIP neuroproliferation.[14,17]

Chronic mild stress during adolescence, another time of rapid brain development, results in behavioral and physiological differences in adulthood for female, but not male rats.[51-54] Interestingly, adolescent female rats seem more resilient to acute or chronic stress than their male counterparts, but are unable to recover as thoroughly from chronic stress regimens and are more likely to display differences in adulthood. Adult female rats exposed to chronic stress during adolescence have elevated basal CORT, but a blunted increase in plasma CORT in response to acute stress,[53] reduced cell survival and proliferation in the DG,[54] and depressive-like behaviors in the forced swim test (FST),[53] as well as sensitivity to nicotine with regards to locomotor activity.[51,52] The sexually dimorphic responses to adolescent stress implicate E_2's organizational role in female vulnerability to MDD, possibly through stress mitigation during rapid development that results in permanent disruption of the HPA axis.

HPA axis dysfunction can be described as an overactive stress response resulting in elevated free CORT and down regulation of HIP glucocorticoid receptors (GR),[52] limiting the functionality of negative feedback mechanisms to stress response and free CORT. While elevated CORT due to stress response is temporary in adult rats, there is evidence that chronic stress during adolescence, the time of HPA axis maturation, results in persistent HPA axis dysfunction in adulthood,[51,54] and differentially affects females but not males.[54] While adolescent male rats exposed to chronic mild stress display increased stress responses such as attenuated weight gain and elevated CORT[53,54] compared to adolescent female rats exposed to the same stress regimen, the stress responses displayed by the males do not persist into adulthood. Females, however, display depressive-like behaviors such as reduced sucrose preference in the sucrose preference test and increased immobility in the FST, as well as physiological differences such as elevated basal CORT and decreased DG cell proliferation and survival in adulthood, but not in adolescence. The sexually dimorphic responses to chronic stress in adolescence may be attributable to the developmental timeline of the HPA axis, as female rats develop sooner than males, and increasing basal CORT during adolescence may decrease acute stress

response by rapidly down-regulating glucocorticoid receptors (GR) in a manner that persists into adulthood. However, it should be noted that activation of the β estrogen receptors (ERβ) increases cAMP response element-binding protein (CREB),[55] a transcription factor that regulates production of corticotropin releasing factor (CRF) as well as BDNF. ERβ activation reduces stress-related CORT,[56] while increased E_2 and activation of the β estrogen receptors (ERβ) increase it.[57] While the relationship between fluctuating sex hormones and HPA axis development has yet to be defined, it is possible that E_2 can buffer the stress response by mediating down-regulation of the GR and/or CRF receptors. As females have significantly higher endogenous estradiol than males, then estrogenic mitigation of chronic stress during HPA axis development may be responsible for the establishment of persistent CRF/CORT desensitization for females, but not for males.

Acetylcholine

The cholinergic system has been implicated in MDD, although its role in mood regulation[15,58-62] and memory formation[15,59,60,63] is not clearly defined. Figure. 01 briefly illustrates the purported relationship between modulation of nAChRs and MDD and memory, as well as estrogenic involvement that is discussed later. As shown in Figure. 01, physostigmine, an acetylcholinesterase inhibitor that indirectly facilitates acetylcholine neurotransmission, can cause symptoms of depression.[59,61,64] However, nicotine, a nicotinic acetylcholine receptor (nAChR) agonist, has been shown to relieve symptoms of depression,[59,60,61,65,66] and decrease depressive-like behaviors in rats.[59,65,67] Chronic usage of nAChR agonists such as cytistine and varenicline (used clinically for smoking cessation) may have mood enhancing effects, but may also increase suicidality.[59] Many marketed antidepressants that demonstrate efficacy in MDD, including tricyclic antidepressants and selective serotonin reuptake inhibitors, have been shown to be nAChR antagonists at the prescribed doses.[61] Mecamylamine, a nAChR antagonist, has been studied extensively for its antidepressant effects in rodents[62] and humans[8,61] Furthermore, muscarinic acetylcholine receptor (mAChR) antagonists such as scopolamine have been shown to reduce depressive-like behaviors[15] and to act as effective short-term antidepressants in rodents.[15,58,59] As both acute administration of antagonists or partial agonists[59,67] and chronic administration of agonists result in mood enhancement, it is likely that the mechanism of antidepressant-like action is receptor blockade and acetylcholine (ACh) desensitization rather than receptor activation.

Interestingly, both the muscarinic and the nicotinic cholinergic systems are involved in memory formation. High doses of scopolamine can be used to cause anterograde amnesia,[63] and nAChR β_2 knockout mice show HIP atrophy and significant spatial learning impairment,[60] reminiscent of MDD patients. Additionally, physostigmine increases N-methyl-D-aspartate (NMDA) receptor binding in the CA1 region of the HIP, which corresponds with working memory enhancement.[68] This increase in NMDA receptor binding and resulting working memory enhancement is comparable to that caused by E_2,[68,69] which, in addition to being a sex hormone, is neurotrophic[70] and has nootropic (cognitive and memory enhancing) properties and cholinergic involvement.

17ß-Estradiol (E_2)

Administration of E_2 has been shown to relieve MDD in depressed, perimenopausal patients[27,71] and reduce depressive-like behaviors in rats.[67,72] Ovariectomized (ovx) rats, and intact female rats administered estrogen receptor (ER) antagonists intracranially to the HIP display increased anxiety-like and depressive-like behaviors, which are reversed by administration of E_2 or selective estrogen receptor modulators (SERMs).[22] Additionally, SERMs that increase ER activity have been shown to have antidepressant-like effects in rats.[73-75] Figure. 01 illustrates the pathways by which E_2 enhances mood and memory via ERβ and GPER (G-protein coupled estrogen receptor). Also shown, selective estrogen receptor β modulator (SERMβ) diarylpropionitrile (DPN) activation of ERβ independently decreases depressive-like behaviors and enhances memory.

As stated previously, E_2 has both nootropic and neurotrophic properties. Due to this, E_2 has been studied as a potential treatment for some cognitive disorders such as Alzheimer's disease (AD), a neurodegenerative disorder with significantly higher incidence in women than in men.[76-78] There is evidence that perimenopausal E_2 replacement therapy (ERT) may be protective against AD[77-80] and that long-term treatment reverses some, but not all, of the cognitive impairments in postmenopausal women with AD. E_2's nootropic effects also occur in the absence of neurodegenerative dementias. ERT to postmenopausal women has been found to enhance their performance in the HIP-dependent Spatial Working Memory (SPWM) test,[81] as well as other forms of reference memory[82-85] and working memory.[69,80] Reference memory in rats improves with ERT.[86-90] Furthermore, long-term ERT has been shown to increase extracellular HIP acetylcholine in ovx rats.[91] Ovx rats display reduction of HIP acetylcholine receptors that is reversible by administration of E_2,[70] and ERT protects against progressive neurodegeneration caused by AD in ovx rats and mice.

The pattern of E_2-potentiated ACh release[91,92] and cholinergic involvement in HIP-dependent memory enhancement by E_2 suggests a regulatory role for E_2, wherein E_2's modulation of the cholinergic system may be responsible for enhancing memory (Figure. 01). As chronic agonism of nAChRs has been shown to have antidepressant effects,[59] it is possible that mood enhancement subsequent to E_2 administration may be partially due to desensitization of the nAChR by E_2-induced ACh elevation.

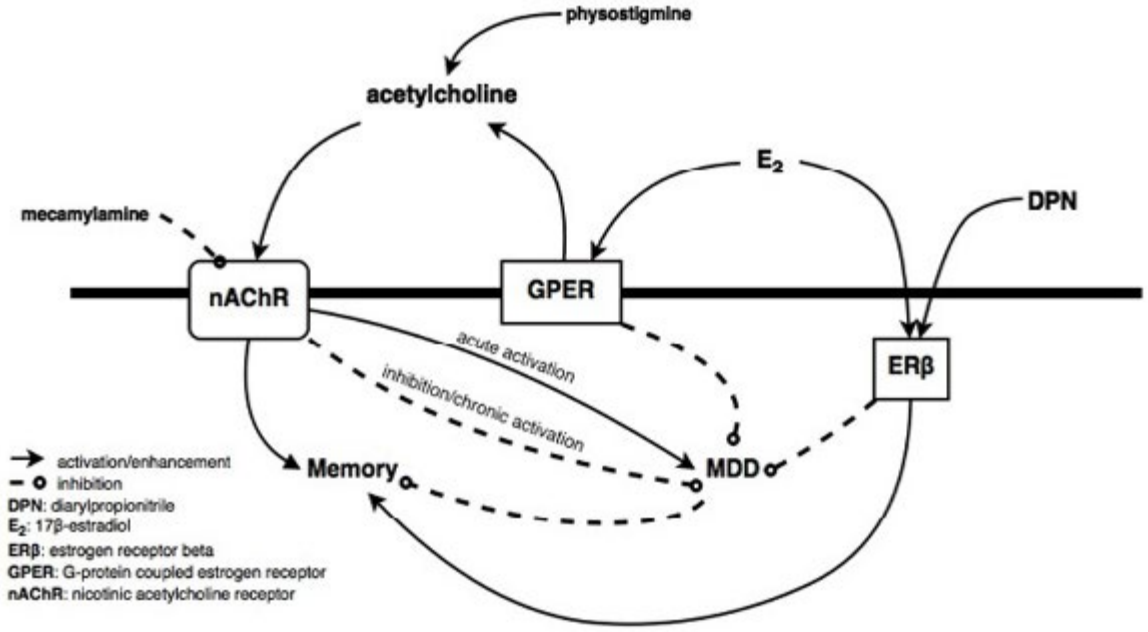

Figure. 01 *Relationship between modulation of nAChRs and MDD and memory*

E_2 also has rapid effects on behavior, as it has been shown to cause antidepressant-like effects[67] and memory enhancement in rats as quickly as three minutes after injection.[85] It is possible that the acute effects of E_2 involve modulation of ACh activity. ERs are known to colocalize with mAChR and nAChR in rat neuronal[93,94,95] and astrocyte cultures. As activation by selective ligands for ERα, ERβ, or either family of cholinergic receptors can cause astrocyte depolarization,[96] it is likely that activation of these neuronal receptors will also

cause depolarization and subsequent neurotransmitter release. Acute administration of E_2, potentiated by the selective 5-HT1A agonist 8-hydroxy-2(di-n-propylamino) tetralin, enhances acetylcholine release in rats,[92] and release of HIP acetylcholine in rats was shown to be stimulated by acute administration of E2 when combined with maze training.[97] Furthermore, E_2 has been shown to enhance potassium-stimulated release of HIP Ach[91] via actions at G protein-coupled estrogen receptor 1 (GPER).[94] GPER primarily binds E2 and is localized in the endoplasmic reticulum, the Golgi apparatus, and the nuclear membrane,[98] and is preferentially expressed on cholinergic neurons in both rats and rhesus monkeys.[94,95] Interestingly, antagonism of the muscarinic 2 (M2) receptor inhibits both estradiol-induced and physostigmine-induced increase in CA1 NMDA receptor binding,[68,69] indicating that estradiol's memory enhancements are partially dependent upon ACh activation of M2 receptors. However, as increased ACh activity is associated with symptoms of depression,[8,59,64] then some portion of the rapid antidepressant-like effects of E_2 and activational SERMs must be independent of ACh.

Estrogen Receptors

There are two known subtypes of nuclear estrogen receptors (ER), and one non-nuclear receptor. Both nuclear receptors, ERα and ERβ, act as transcription factors[55] as well as mediate nongenomic, rapid responses, and have been shown to be involved in memory acquisition in mice[55,99-102] and in rats. Both ERα and ERβ have been implicated in modulating nociception in mice[103] and promoting neuroprotection in HIP cell culture by increasing antiapoptotic protein Bcl-2.[104] The chemotherapeutic agent tamoxifen, an ERβ antagonist and a partial ERα agonist,[105] partially blocks the neuroprotective effects of E_2 administration in rats[70,105] and significantly reduces learning acquisition and retention in ovx mice[99] ERα has been shown to be involved in emotional memory acquisition in rats[100] and mice[106] during the inhibitory avoidance task.[100,106] Additionally, ERα has been shown to regulate proceptive sexual behaviors, such as lordosis, in female mice,[107] and rats[108,109] and parental behaviors, including some aggressive behaviors, in female mice, and there is evidence for a developmental role of ERα activation in the regulation of these behaviors.[107] ERα gene polymorphisms have been correlated with increased risk for post-partum depression,[110] a form of MDD that definitively occurs after giving birth. ERα gene polymorphisms have also been correlated with major depressive episodes in elderly women, however, half of the depressed women experienced their first major depressive episode postmenopausally, and the type of depression experienced premenopausally by the remaining half was not clarified.[111] Alternatively, other research found no increase in ERα gene polymorphisms in adolescent girls who had recently experienced their first major depressive episode,[112] suggesting that ERα's role in depression may be related to reproductive events resulting in low free E_2.

Additionally, decreases in ERα function during conditions of low free E_2 such as aging, may contribute to age-related cognitive decline and possibly amyloidosis.[113] Loss of ERα function may be due to ERα polymorphisms or age-related increase of ERα splice variants, and result in a lower ERα to ERβ ratio and a relative increase in inhibition of ERα-related transcription by ERβ modulation.[113] Thus, reducing the neuroprotective effects of ERα and subsequently increasing risk of age-related cognitive impairment. However, there is evidence that ERα does not mediate HIP-dependent learning in young, gonadally intact rats,[101] or in young ovx mice,[55] and thus is unlikely responsible for MDD-related impairment of visuospatial learning,[7] and verbal and visual recognition memory.[39,40]

GPER, the G-protein coupled non-nuclear ER, is poorly characterized and its roles are poorly defined. It is found in abundance in peripheral cells as well as in brain structures believed to be involved in mood regulation, such as the HIP,[41,75,98] and primarily binds E_2 in the endoplasmic reticulum, the Golgi apparatus, and the

nuclear membrane, rather than the plasma membrane. GPER plays a regulatory role in many physiological functions, including reproductive tissue development, inflammation, nociception, and cell proliferation, as well as potentiating potassium-stimulated ACh release in the HIP and other brain areas.[94] GPER also plays a role in estrogenic mood regulation, although this role has not been delineated. GPER activation is responsible for E_2-related increase of anxiety-like behaviors in the open field in ovx and intact male mice, but also inhibits stress response to adrenocorticotropic hormone (ACTH) and reduces depressive-like behaviors in mice[75] Unsurprisingly, antagonism of GPER impairs E_2's antidepressant effects. Whether SERMs thought to be acting at ERα or ERβ are actually interacting with GPER, or at multiple ER, is currently being investigated for many systems. As yet, much of the data is superficially conflicting. For example, the classical ER antagonists tamoxifen and ICI182 have been shown to agonize GPER, and propylpyrazoletriol (PPT) activation of ERα often results in similar cellular responses as GPER activation by the selective agonist G-1. However, DPN activation of ERβ does not exhibit these effects. Depending on the system being studied, the effects of DPN are either independent of or in direct opposition of the effects of G-1.[114] Whether correlations between activity at ERα and GPER are due to the binding of ligands at both receptors, or to shared downstream effects, such as the activation of extracellular-signal-regulated kinase, is unclear,[114,115] as is whether SERMβ also interact with GPER as partial or inverse agonists. However, as adolescent girls suffering from first onset of MDD display more ERβ gene variants[112] and significantly less ERβ mRNA[116] compared to non-depressed women, GPER activity is unlikely to be solely responsible for estrogenic mood regulation. Furthermore, tamoxifen, which antagonizes ERβ but is a GPER agonist and a partial agonist of ERα, blocks the neuroprotective effects of E_2 in rats[70,105] and impairs learning in ovx mice.[99] Perhaps the GPER-mediated ACh release in HIP[90,93] contributes less to E_2's positive effects on memory than as-yet-undefined actions of ERβ activation.

Estrogen Receptor β (ERβ)

ERβ has not been shown to be involved in reproductive behaviors in mice[107] and rats,[100,108,109] but has been implicated in mood and memory regulation. Adolescent girls tested after the first onset of MDD commonly display ERβ variants, but standard genes for ERα,[112] and ERβ mRNA are reduced in suicide victims.[116] In addition to the nucleus, where ERβ acts as a transcription factor,[85] ERβ can be found in the mitochondria,[117] dendrites, axons, and axon terminals of rat HIP neurons,[118,119] as well as in non-nuclear regions of HIP astrocytes.[96] E_2 treatments increase synaptic ERβ in ovx rats,[120] likely due to rapid translocation of bound ERβ from the nucleus towards the plasma membrane such as is seen in HT22 cells (immortalized mouse HIP cell line) and primary mouse cortical neurons.[121]

Selective ERβ agonists have been shown to be anxiolytic in rats[108] and mice,[102] to promote synaptic plasticity by increasing CREB phosphorylation in mice,[55] as well as increase cell survivability.[123] ERβ has also demonstrated modulation of HIP-dependent memory acquisition in mice[55,101] spatial memory acquisition in rats[100] and mice,[100,102] and promotion of neurogenesis in mice[101-123] and HIP cell culture.[104] Additionally, ERβ activation enhances long-term potentiation (LTP) in HIP CA1 area, which has been implicated in contextual recognition memory. Unpublished data from our laboratory found DPN to have a rapid antidepressant-like effect in ovx rats more robust than that of E_2.[67] Our results indicate that the DPN-induced antidepressant-like effects may be attributable to both serotonin and norepinephrine activity, as measured by increased swimming and climbing behaviors in the FST, which is indicative of serotonin and norepinephrine transmission, respectively.

Estrogen receptor β knock out (βERKO) mice have been a valuable model for studying the role of ERβ in mood and memory. Administration of both E_2 and DPN have been shown to enhance spatial recognition

memory in rats and wild type (WT), but not in βERKO mice,[74,102] effectively identifying ERβ as a mediator of E_2's spatial memory enhancement effects. βERKO mice have impaired memory acquisition ability[73,101] and reduced synaptic plasticity as well as high anxiety-like behaviors.[74] βERKO mice are nonresponsive to E_2 treatment and display no reduction of depressive-like or anxiety-like behaviors or enhancement of memory. Both male and female βERKO mice, which are comparable to WT cohorts during infancy, experience progressive lifetime neurodegeneration and astrocyte remodeling, resulting in significant brain volume reduction,[125] suggesting that ERβ plays a developmental role in the central nervous system (CNS), as well as modulating neuronal proliferation and glial survivability.

Discussion

The disparate ratio of MDD in women and men points to a universal gender-specific influence on mood regulation, one that transcends cultural and ethnic groups[126] and affects women primarily during years of reproductive capability. The times of greatest increased incidence of MDD correspond to times of physical and social change, specifically puberty, postpartum, and perimenopause, in which not only a woman's body is changing, but her role and responsibilities. It can be argued that the increased incidence of MDD is attributable to the stress of women's gender roles, especially during parenting. Caring for children is a great responsibility, the burden of which is disproportionately placed upon females, whether or not they live with a co-parent.[127] For example, the weekly housework for new mothers increases by an average of 9.07 hours, but new fathers only do an additional 1.04 hours of housework per week. Interestingly, while nearly all parents living with minor children are more likely to report symptoms of depression than childless counterparts,[128] the influence of parenthood as a risk factor for MDD is not significantly different for women than for men, and becoming a parent after the age of 23 has been correlated with reduced risk of developing depression in both sexes.[129] In fact, education level, employment, and socioeconomic status are more influential in the risk of developing symptoms of depression than being a parent,[127-129] none of which explain the increased incidence of MDD in women, or the physiological differences in MDD patients.

In addition to its protective effects previously noted, investigations into the influence of E_2 on stress response in adulthood primarily use ovx rats, which display more depressive-like behaviors,[22] impaired spatial memory, and decreased neurogenesis, the degree to which correlates positively to the length of time spent ovx.[84] Similar to the pattern seen in AD women,[76] long-term administration of E_2 protects against cognitive impairment and enhances working spatial memory in both young and old ovx rats,[130] and endogenous E_2 has been found to enhance working spatial memory tasks in rats after 21 days of chronic mild stress.[89,131] E_2 administration enhanced performance for both females and males, while the same stress regimen impaired male adult rats and had no effect on ovx rats. Notably lacking are investigations into the effects of prepubertal ovx on adult HPA axis function, depressive-like behaviors, and HIP volume. Considering the exhaustive evidence that early-life and adolescent stress greatly increases female risk for adult impairments in mood and memory,[4,17,20,28,49,51] the influence of E_2's organizational effects is a compelling subject of inquiry. As E_2 has been shown to be neuroprotective and enhance mood and memory in adulthood by interactions at ERβ, might SERMβ administration during or after adolescent chronic stress protect against HPA axis dysfunction and the development of depressive-like behaviors and cognitive impairments in adulthood?

Adult women may benefit from research into novel estrogenic treatments as well. Hormone therapy (HT) contains E_2, which has equal affinity for ERα as ERβ. E_2 has been shown to work synergistically with the selective serotonin reuptake inhibitor (SSRI) fluoxetine to potentiate antidepressant-like effects at sub-clinically low

doses, and middle-aged female rats respond weeks sooner than young adult females.[72] While the synergistic mechanism has yet to be identified, SERM/SSRI cocktails have the potential for relatively rapid-acting antidepressant treatment with minimal adverse effects. ERβ modulates mood and memory,[55,73,101,104,112,116,122,124,] enhances synaptic plasticity,[55,123] and cell survivability. Unlike ERα, ERβ does not modulate sexual, parenting, or aggression behaviors,[100,107,108] and so SERMβ antidepressant cocktails are less likely to have unwanted side effects, such as menstrual cycle involvement, than HT using E_2. Additionally, recent and as-yet-unpublished research from our lab found acute administration of both DPN and cytisine to independently and in combination decrease depressive-like behavior in ovx rats. When DPN and cytisine were administered concurrently, the antidepressant-like effect was additively greater than that elicited by either DPN or cytisine alone. This suggests that the acute antidepressant-like effect of DPN is partially independent of nAChR activity, and that SERMβ have the potential for both acute and chronic antidepressant effects. Further study of ERβ's short- and long-term modulation of mood and memory is warranted, particularly in intact, rather than ovx, animal models of depression that display both impaired spatial memory and increased depressive-like behaviors. If indeed, SERMβ are shown to be efficacious antidepressants, alone or in conjunction with other drugs, novel pharmacotherapeutics can be developed that target the ERβ pathway, thereby reducing the period of latency until relief and increasing the overall quality of antidepressant effects.

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