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Review

Estrogen in prefrontal cortex blocks stress-induced cognitive impairments in female rats

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ABSTRACT

Animal and human studies have found that males and females show distinct stress responses. Recent studies suggest the contribution of estrogen in the brain to this sexual dimorphism. Repeated stress has been found to impair cognitive behaviors via suppressing glutamatergic transmission and glutamate receptor surface expression in pyramidal neurons of prefrontal cortex (PFC) in male rats. On the contrary, female rats exposed to the same stress paradigms show normal synaptic function and PFC-mediated cognition. The level of aromatase, the enzyme for the biosynthesis of estrogen, is significantly higher in the PFC of females than males. The stress-induced glutamatergic deficits and memory impairment are unmasked by blocking estrogen receptors or aromatase in females, suggesting a protective role of estrogen against the detrimental effects of repeated stress.

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1. Sexually dimorphic effects of stress and role of estrogen

Corticosteroid stress hormones serve as a key regulator of cognitive and emotional processes [20,43]. It has been proposed that there is an “inverted U” relationship of stress to cognitive function [22], such that a moderate level of corticosteroid has pro-cognitive effects, while too low or too high corticosteroid levels are detrimental to cognitive processing [27]. Our group has found that stress exerts dual effects on cognition through bi-directional modulation of glutamatergic transmission in prefrontal cortex (PFC), a key target region of stress hormones. In young (~4 weeks old) male rats, acute stress significantly enhances glutamate receptor-mediated synaptic currents and improves working memory [75,76]. Conversely, young male rats exposed to one-week repeated restraint or unpredictable stress show the

diminished PFC glutamatergic transmission and the impaired PFC-mediated cognitive function, temporal order recognition memory (TORM, [77]).

While these findings support the notion that short-term (acute) stressors elicit adaptive and beneficial changes, whereas long-term (chronic) stress results in maladaptive and deleterious effects, this pattern of stress responses appears to apply to only males. In response to one acute stressful event of intermittent tail-shocks, spine density is enhanced in the male hippocampus but reduced in the female hippocampus [62]. When the subchronic stress challenge, which induces cognitive impairment in males [77], is introduced to young female rats, their glutamatergic transmission in PFC and TORM function are unaffected [70, Fig. 1A]. Similar sex differences to chronic stress have also been reported by other groups. For example, in male rats, restraint stress (6 h/day, 21-day) impairs performance on a variety of spatial memory tasks including radial arm maze, object placement, Y-maze, water maze, and a nonspatial, recognition memory test [6,7,17,31]. In contrast, females exposed to the same stress paradigm show

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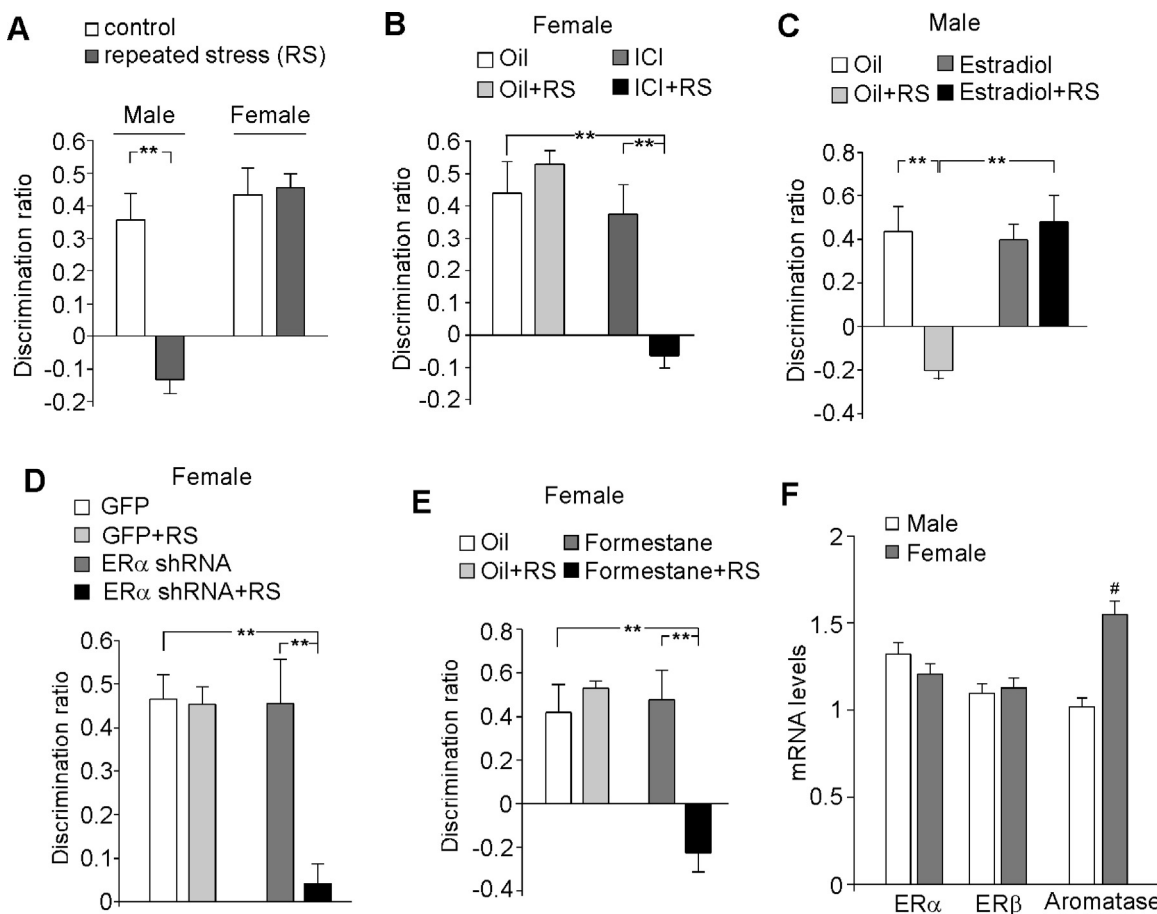


Fig. 1. Estrogen protects against the detrimental effects of repeated stress on cognition. (A) Bar graphs (mean \pm SEM) showing the discrimination ratio (DR) of temporal order recognition memory (TORM) tasks in control or repeatedly stressed (restraint, 7-day, RS) male or female rats (4-wk-old). (B and C) Bar graphs showing the DR of TORM tasks in control vs. repeatedly stressed females with injections of the ER antagonist ICI182,780 (B, 0.05 mg/kg, s.c.), or males with the injections of the ER agonist estradiol (C, 0.1 mg/kg, s.c.). (D and E) Bar graphs showing the DR of TORM tasks in control vs. repeatedly stressed females with the PFC injection of GFP or ER α shRNA lentivirus (D), or with the injections of aromatase inhibitor formestane (2 mg/kg, s.c.). **: $p < 0.005$, ANOVA (A–E). (F) Quantitative real-time RT-PCR data on the mRNA level of ER α , ER β and aromatase in PFC from male vs. female rats. #: $p < 0.05$, *T*-test. Adapted from Wei J, et al., Mol. Psychiatry, 19: 588–598, 2014.

enhanced cognition and memory in almost all of these tasks [7,12,10,9,8,44,18,31]. These animal studies suggest that females are more resilient to chronic stress than males, at least in terms of the measured cognitive behaviors [16].

Interestingly, when estrogen receptor (ER) function is blocked in female rats, the detrimental effects of repeated stress (2-h restraint, 7-days) on PFC glutamatergic transmission and TORM function are unmasked [70], Fig. 1B). On the other hand, when estradiol is administered in male rats, they become resilient to the same stressor [70], Fig. 1C). It suggests that an estrogen-mediated mechanism makes females less susceptible to the deleterious effects of repeated stress than males.

However, the role of estrogen in stress responses is not without controversy. There are also reports suggesting that estrogen may amplify the stress responses in females. Activating stress systems pharmacologically by FG7142, a benzodiazepine inverse agonist, induces impaired PFC working memory in females during proestrus (high estrogen), but not during estrus (low estrogen), suggesting that estrogen may increase the sensitivity to stress in females [60]. Estrogen replacement in ovariectomized female rats exposed to a behavioral stressor (2-h immobilization for 10 days) also induces the greater dendritic remodeling in PFC neurons projecting to the basolateral nucleus of the amygdala (BLA) [61]. Preclinical studies using fear conditioning and extinction paradigms have found that females with low estrogen levels exhibit

impaired extinction retrieval [45,46], which can be reversed by stimulation of D1 dopamine receptors [58]. It suggests that estrogen might influence PFC-BLA function in part through dopaminergic mechanisms.

Converging evidence supports that females and males exhibit different biochemical, cellular and behavioral effects of stress [62,37,11,40,5]. However, the observed sex differences of stress responses and role of estrogen could be affected by a number of factors, such as animal strains, animal ages, stress paradigms, estrogen regimen, and measured outcomes.

2. Resilience vs. vulnerability of females to stress-related mental disorders

Epidemiological studies indicate that women are more likely to develop stress-associated mental disorders, such as depression and PTSD [71,14]. Therefore, it is easy to assume that females have higher stress susceptibility. However, it is important to note that gender vulnerability in stress responses is different from gender vulnerability in mental disorders. Despite the stress exposure for almost everyone, only a small population develops stress-associated mental disorders, including depression and PTSD. Genetic risk factors carried by the susceptible individuals are likely to play a causal role, while stress may only serve as a trigger to precipitate a variety of emotional and cognitive difficulties.

Genetic factors probably also directly influence the intrinsic sensitivity to stress, which contributes to the pathogenesis of psychiatric diseases [28]. Recent studies suggest that individuals carrying Vall66met allele of the *BDNF* (brain derived trophic factor) gene have the altered vulnerability to stress and antidepressant responses [74]. Epigenetic mechanisms involving chromatin remodeling and gene expression could also influence stress sensitivity [65,67].

There are two peaks of depression prevalence in women: postpartum depression, and perimenopausal depression, both of which are associated with large drops (postpartum) or excessive fluctuations (perimenopausal) of serum estradiol levels. Human PET imaging studies suggest that estrogen decline during perimenopausal age elevates the level of monoamine oxidase A, a neurobiological change that also presents during major depressive episodes [57]. The critical role of estrogen in mood disorders is also supported by animal studies. It has been found that injecting estrogen reverses helplessness in animal depression models and enhances hippocampus plasticity [24,13]. Females are more responsive to the action of antidepressants than males [23]. Corroborating with the role of estrogen in females' stress resilience [70], estrogen also shows anxiolytic and antidepressant effects in animal models, which are dependent upon the utilized regimen of estrogen and interactions with the hypothalamic–pituitary–adrenal axis [68].

3. Role of estrogen in synaptic regulation and brain diseases

One surprising finding is that the stress resistance in females is unchanged by ovariectomy that only terminates the ovarian estrogen, but is blocked by knockdown of ER α only in the PFC region [70, Fig. 1D] or global inhibition of aromatase, the estrogen synthesis enzyme [70, Fig. 1E], implying that CNS-synthesized estrogen [72,32] may determine the sexually dimorphic vulnerability to stress. Consistently, it has been shown that estrogen can be synthesized by aromatase localized in neurons from endogenous cholesterol [26]. Moreover, ischemic neuroprotection in females has been attributed to the local, nongonadal estrogen, which may be aromatized from precursor androgens [39]. The expression of aromatase is significantly higher in PFC neurons of female than male rats [70, Fig. 1F], suggesting that pre-pubertal female PFC has an endogenous capacity to generate estrogen that provides protection against repeated stress.

The protective effect of estrogen against stress is in line with the critical role of estrogen in neurogenesis [52], synaptic spine growth [24] and memory consolidation [59]. Depriving estrogen in rats induces postpartum–depression symptoms, and altered expression of genes involved in learning and memory [66]. It has been found that estrogen protects females from several neurological diseases, including seizure [56], ischemia [54] and Alzheimer's disease [36]. Studies suggest that estrogen receptor (ER α), which is expressed at synapses of hippocampus [1] and PFC [69], influences synaptic function through a non-genomic mechanism [41]. For example, estrogen potentiates the activation of NMDA receptors and voltage-gated calcium channels, which results in the increased calcium influx and new excitatory synapses in hippocampus [73,42]. Intracellularly, estrogen rapidly activates synaptic Akt that facilitates local synthesis of PSD-95, a scaffolding protein required for spinogenesis [2]. Moreover, estrogen activates RhoA–ROCK–LIMK–cofilin signalling pathway that controls actin polymerization involved in spine growth [64,33]. At circuitry level, estrogen suppresses inhibitory GABAergic interneuron by downregulating *BDNF* synthesis, which indirectly increases excitatory synaptic transmission of pyramidal neurons in hippocampus [48].

Recent studies have uncovered new functions of brain-derived estrogen (17 α estradiol). This neurosteroid can be produced in

hippocampus [30]. It is proposed that estrogen exerts its action in various brain regions through a combination of genomic and nongenomic mechanisms. Unlike the sustained effect of ovarian estrogen, injection of 17 α estradiol in ovariectomized animals rapidly induces hippocampal spine formation without increasing the expression of synaptic proteins [64]. Electrophysiological data suggests that 17 α estradiol exerts an immediate effect on glutamatergic transmission by enhancing presynaptic glutamate release [63].

4. Sexual dimorphism in developing brain

Evaluation of the distribution of ER α and ER β has revealed their presence in diverse brain regions (cerebral cortex, basal forebrain, amygdala, etc) through early postnatal periods (p3–p14), supports a potential role for estrogens in neural development [53]. Our study shows that estrogen protects prepubertal females from the detrimental effects of repeated stress [70], suggesting that estrogen plays a role in developing female brains, rather than being a typical sex hormone for reproduction. In agreement with this, mounting studies pinpoint the sexual dimorphism in brain development. For instance, comparing to neurogenesis in females, males have a higher proliferation rate and a better survival rate of de novo neurons [78]. Imaging study indicates that white matter development is strongly influenced by hormonal environment of estrogen during early postnatal period, but is minimally affected later in life [34]. Significantly decreased levels of ER β and aromatase (the enzyme converting testosterone to estrogen) have been found in PFC of human subjects with autism spectrum disorders [15], which may be linked to the elevated testosterone effects on arousal and social anxiety [55], and contribute to male predominance in autism.

Why are there gender differences in brain development and function? Genetic information encoded in the sex chromosome has been suggested as an underlying reason. For example, the *SRY* gene on Y chromosome underlies sex-dependent neuroanatomical structures in various brain regions, as well as behavioral phenotypes, such as social exploration and aggression [21,25]. Other theories suggest that females' additional X-chromosome may provide the pattern of X-linked gene effects that is different from males [19].

Besides genomic influence, epigenetic factors also play a key role. Estradiol regulates its own receptor function via DNA methylation on the promoters of ERs, which is thought to contribute to the sexual dimorphism of neuronal anatomy and behavior [50]. Consistent with this, knockdown of ER with antisense oligonucleotides disrupts sexual differentiation of the brain [38]. ER knockout female mice display diminished maternal behaviors and exhibit male-like aggressive behaviors [51].

Postnatal stress is thought to affect the ability to cope with adversity in adulthood [3]. Emerging evidence suggests that the vulnerability to stress in developing brains is also gender-dependent. Study of prenatal stress shows that male, but not female, offspring exposed to stress in early pregnancy have maladaptive stress responses, which is associated with alterations in corticotrophin-releasing factor (CRF) and glucocorticoid receptor (GR) expression [47]. Female offspring is more resilient to various early life stress challenges than male offspring [35]. When exposed to postnatal stress, such as early weaning from maternal lactation or limited nesting & bedding materials, neurogenesis is perturbed in male, but not female, animals [29,49]. Such gender-dependent susceptibility to stress during development may be linked to mental illnesses in adult life [4,19].

In summary, animal and human studies have found that males and females show distinct stress responses and have different vulnerability to stress-related mental disorders. Recent studies

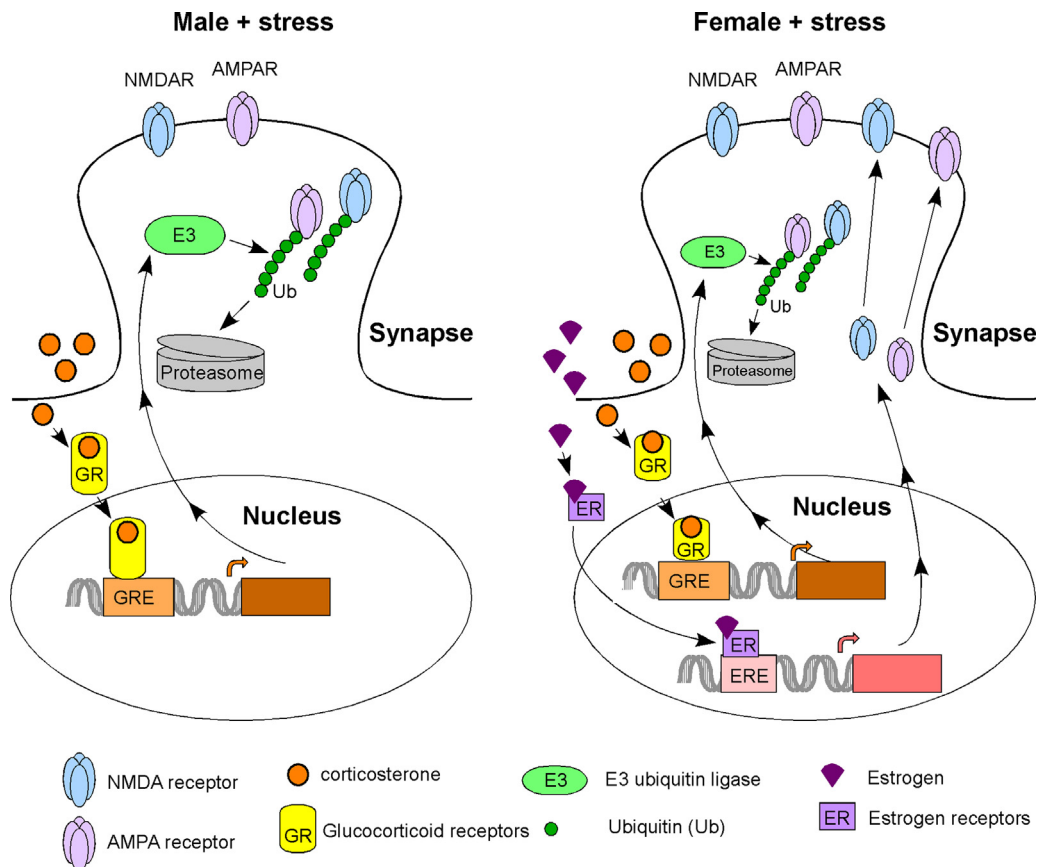


Fig. 2. A diagram showing the role of estrogen in determining the sexually dimorphic effects of stress on glutamatergic synaptic function in prefrontal cortical neurons. In males, repeated stress triggers the activation of glucocorticoid receptors (GR). GR bind to glucocorticoid response element (GRE) on the promoters of downstream genes, triggering the increased glutamate receptor ubiquitination and degradation. In females, estrogen activates estrogen receptors (ER), which bind to estrogen response element (ERE) and enhance the transcription of synaptic plasticity genes that promote the synthesis and exocytosis of glutamate receptors, therefore counteracting the stress-induced depressing effects.

have suggested the contribution of estrogen in the brain to this sexual dimorphism. The differential effects of stress on glutamatergic transmission in males vs. females, which are attributed to the influence of estrogen on synaptic plasticity (Fig. 2, [77,70], may underlie the sex-specific impact of stress on cognitive processes. More detailed genetic, epigenetic and molecular mechanisms await to be elucidated.

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