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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.

Contents

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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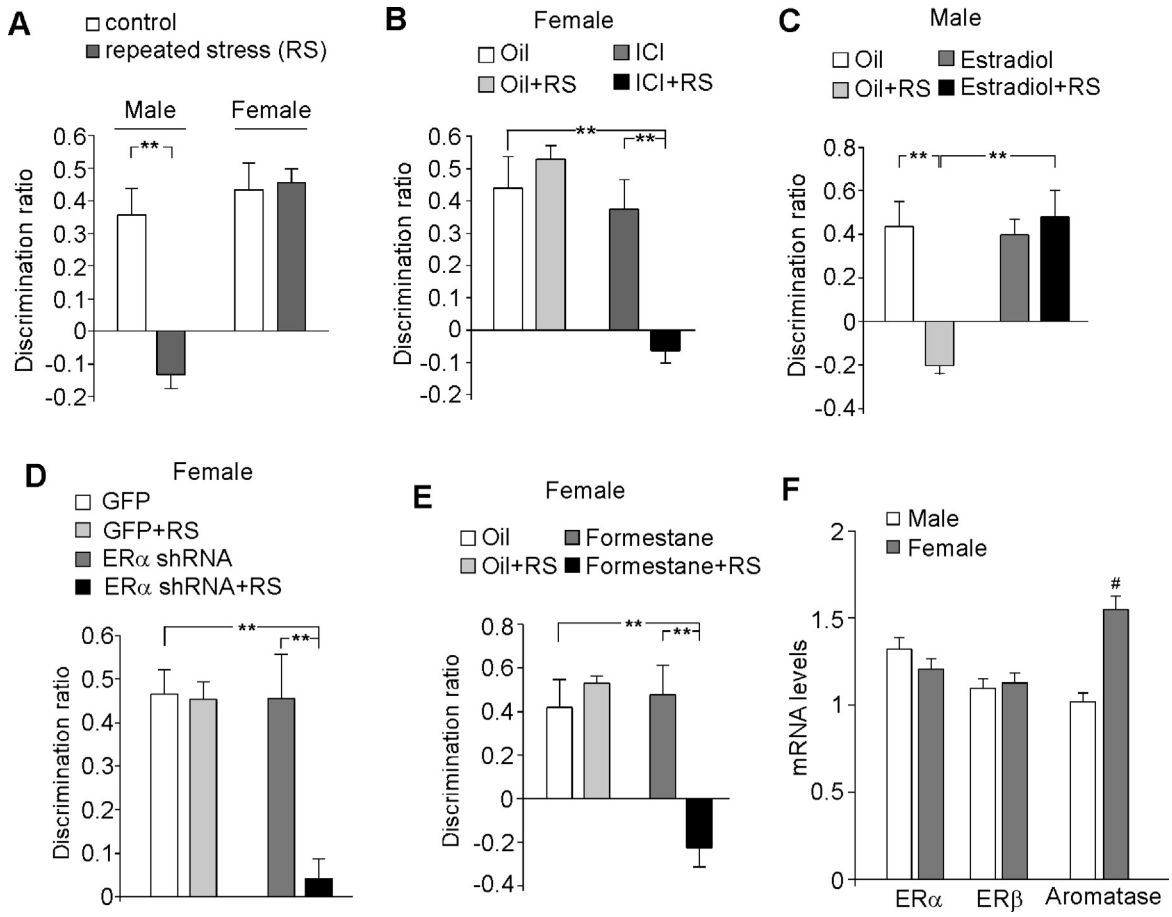

Fig. 1. Estrogen protects against the detrimental effects of repeated stress on cognition. (A) Bar graphs (mean ± SEM) showing the discrimination ratio (DR) of temporal order recognition memory (TORM) tasks in control or repeatedly stressed (restraint, 7-day, RS) male or female rats (4-wk-old). (B and 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 ERα 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 ERα, ERβ 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.

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