Chronic stress alters local estradiol expression across brain regions in a sex-dependent way

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Why studying chronic stress and estradiol in rodents can inform us about Depression

Why Major Depressive Disorder (MDD) is a significant problem

- Mood disorder
- Global Disease Burden and Impact

- Poor quality of life
- Suicide

Approximately twice as many women as men suffer from MDD

- Transitions involving estrogen fluctuations (puberty, menses, pregnancy, menopause)
- Estradiol (E2): specific type of estrogen
- Suggests that estrogen may be a play a role in MDD risk

Chronic stress (STR) in rodents can model some aspects of MDD symptoms and pathophysiology

MDD symptoms

- Mood swings
- Global Disease Burden and Impact
- Suicide

- Loss of interest
- Difficulty in concentration

- Suggests that estrogen may be a play a role in MDD risk

E2 & cholesterol protect against stress hormone-induced hippocampal neuronal dendritic retraction of castrated male and female rats

Stress Biomarkers: chronic stress reduced body weight gain, but did not alter adrenal size

Inflammatory Biomarkers: chronic stress reduced thymus weight in males and altered cytokines in both sexes

Method: Timeline and Processing

Overview of Findings

Goal 1: Stress and Inflammatory Biomarkers

- See statistically significant
- M: male, F: female

Conclusions and Implications

Chronic stress may alter E2 production within the brain

- Will need to castrate males and females to confirm this hypothesis

- The brain contains enzymes to convert cholesterol into T and E2

- ARO-L expression may be key in understanding sex-specific brain responses to chronic stress: ARO-L is necessary to convert T into E2

- ARO-L may be a potential COMPENSATORY mechanism in the HIPP

- Patter of chronic stress increasing ARO-L vs. control males

- Given that chronic stress leads to hippocampal dendritic retraction in males, HIPP ARO-L increases in males are unlikely to be protective

- ARO-L may be a potential PROTECTIVE mechanism in the mPFC

- Pattern was observed with males showing decreased ARO-L mPFC expression, while females showing increased ARO-L expression.

- The mPFC is highly sensitive to chronic stress, undergoing dendritic changes before the HIPP

- Will need to test by blocking E2 synthesis in this hypothesis

- Synapse remodeling in the HIPP

- Inhibiting ARO-L (via tetraozole), thus blocking E2 production, decreases HIPP dendritic complexity

- These changes can be rescued by administration of E2

Behavioral consequences of inhibiting local E2 production

- Both male and female AROKO (Aromatase-deficient) mice show worse hippocampal and PFC-dependent short-term spatial memory than wild-type mice

- Female ARO KO mice show higher depressive-like behavior than wild-type mice

MDD may be associated with altered local E2 synthesis across brain regions

- Aromatase activity in women affects memory and cognition
- Hormone-based breast cancer chemotherapy that inhibits aromatase (such as letrozole) can impair memory
- Future directions: regional-specific hormonal mechanisms underlying MDD, especially local E2 production via ARO-L

- Measuring brain and serum E2

References


Chronic stress may alter local E2 synthesis in brain regions

- Overview of Findings

- Brain regions of interest include the HIPP, mPFC, AMYG (where STR has been found to induced changes in), and CB (where no STR-induced changes are expected)

- E2 synthesis may be a potential mechanism for stress-induced changes in these regions

- mPFC: STR tended to decrease ARO-L in males, but not in females. AMYG: females tended to have higher ARO-L than did males. CB: expression pattern appeared similar regardless of stress or sex.