Modeling Posttraumatic Stress Disorder in a Genetic Rat Model of Depression

Jenz S, Lim PH, and Redei EE

Dept. Psychiatry and Behavioral Sci., Northwestern University. Feinberg School of Medicine., Chicago, IL

INTRODUCTION

- Posttraumatic stress disorder (PTSD) is an anxiety disorder characterized by exaggerated memory of the traumatic event and high comorbidity with major depressive disorder (MDD).
- Prior stress is known to increase the likelihood of developing PTSD after experiencing a traumatic event[1].
- This study aimed to identify if a genetic animal model of depression shows PTSD-like behavior using the Stress-Enhanced Fear Learning (SEFL) paradigm, which has been used as a model for PTSD.
- Wistar Kyoto (WKY) rats were selectively bred based on their extremes of depression-like behavior[2,3].
- The WKY More Immobile (WMI) strain mirrors many human major depressive disorder specific traits.
- The WKY Less Immobile (WLI) strain is genetically close, but without depression-like behavior.

We hypothesized that previously stressed WMI rats would show increased fear memory and would be an accurate model to further study the relationship between fear memory, depression, and stress.

METHODS

Animals:

- Animals aged 4-6 months were grouped by strain and sex.
- To measure the impact of prior stress, WMI and WLI animals were further divided into two experimental groups, those receiving acute restraint stress (ARS) before contextual fear conditioning (CFC) and the control, who did not (NRS)[2].

Acute Restraint Stress:

- To test the animals' SEFL, one group of WMI and WLI males and females received (ARS) forty-eight hours before CFC, and a second group did not.
- This test acted as a sensitizing event prior to the trauma of CFC.

Contextual Fear Conditioning:

- 48 hours after ARS, rats were placed into an automated fear conditioning apparatus of Technical & Scientific Equipment (TSE, Bad Homburg, Germany) for 3 minutes of habituation, followed by 3 mild shocks (0.8 mA, 1 sec duration, one per minute).
- 24 hours later, the rats were placed in the same environment for 3 minutes without any shocks.
- The times the rat demonstrated a freezing response, a proxy for fear, was tallied during this time.
    - This measure of fear tracked how much memory of the shock the rat retained the second day of CFC.

Plasma CORT levels and hippocampal expression of glucocorticoid (*Nr3c1*) and mineralocorticoid (*Nr3c2*) receptors:

- Plasma CORT levels were measured by ELISA, 48 hours after ARS or NRS before CFC.
- *Nr3c1* and *Nr3c2* expression were measured in the hippocampus of the same animals by quantitative RT-qPCR.

RESULTS

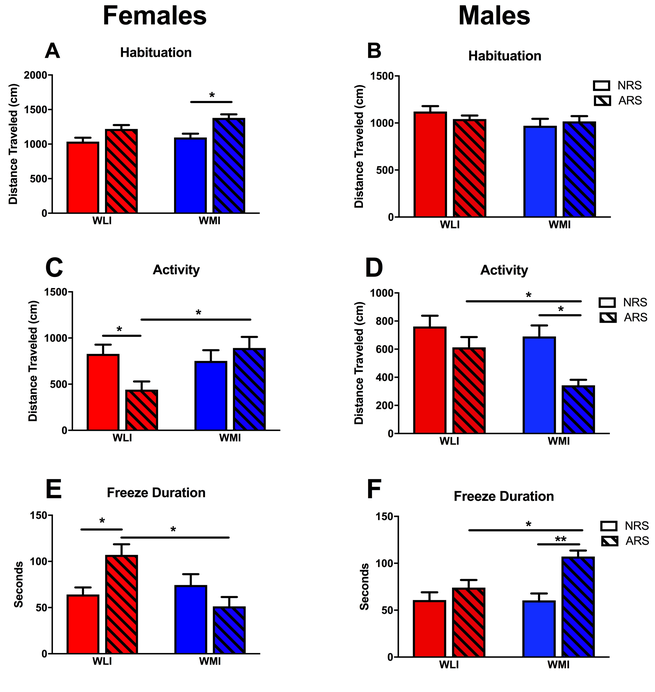

Figure 1: Fear Memory in CFC

A and B. Pre-CFC activity, the distance traveled by females (A) and males (B) during habituation, prior to the shocks, did not differ significantly between strains or acute stress (ARS) and no stress (NRS) animals, except for WMI females, which showed increased activity after ARS.

C and D. Distance traveled on the second day of CFC did not differ between NRS WLI and WMI females and males.

However, WLI females and WMI males showed significantly decreased distance traveled after ARS. Showing the inverse relationship, WLI females and WMI males showed significantly increased freeze duration after ARS.

Values are shown as mean ± SEM; *p<0.05, **p<0.01, post-hoc following ANOVA; #p<0.05 Student's t-test for hypothesis testing.

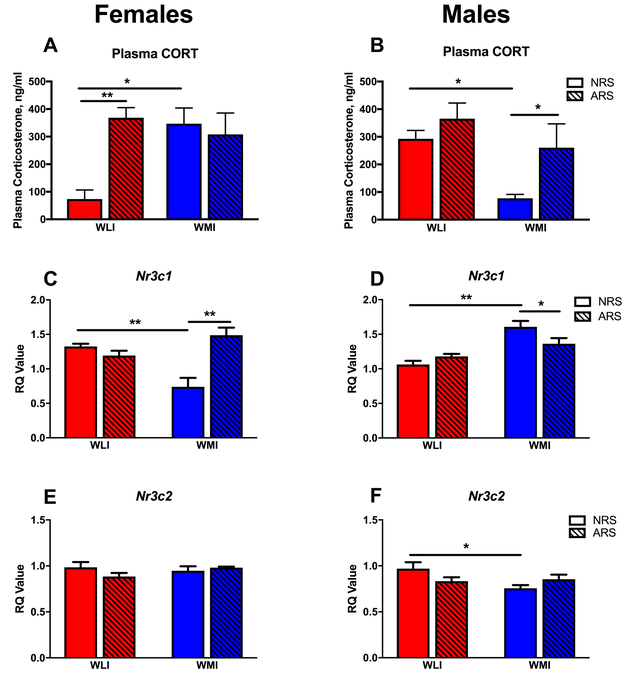

Figure 2: Plasma Corticosterone and Hippocampal Glucocorticoid and Mineralocorticoid Receptor Expression

Plasma CORT levels were significantly higher in ARS WLI females (A) and WMI males (B) than in their NRS counterparts.

Hippocampal *Nr3c1* transcript levels showed inverse relationship to CORT, as expression were increased in NRS WLI females (C) and in WMI males (D).

Hippocampal *Nr3c2* transcript levels showed no significant differences between females (E), but showed decreased expression in control WMI males when compared to ARS WLI males (F).

Values are shown as mean ± SEM; *p < 0.05; **p < 0.01. Abbreviations: NRS, no stress; ARS, acute restraint stress; CORT, corticosterone; Nr3c1, glucocorticoid receptor; Nr3c2, mineralcorticoid receptor.

CONCLUSIONS

- The findings of this study show sex and strain differences in SELF; a model of PTSD.
    - Measures of freeze duration confirmed that male WMI rats demonstrate decreased activity and increased fear memory, while female WMI do not.
    - The reverse was observed for the control WLI strain. WLI females showed decreased activity and increased fear memory, while the male WLI did not.
- Elevation of plasma CORT from lower baseline were found after ARS only in WLI females and WMI males.
- These elevated levels paralleled the high freeze duration responses associated with ARS in female WLIs and male WMIs.
- The lower baseline CORT levels of WLI females and WMI males were inversely related to transcript levels of hippocampal glucocorticoid receptors after ARS.

REFERENCES

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