Peritraumatic Circulating 17β-Estradiol as a Resiliency Factor for Chronic Pain Outcomes in Women Following Trauma

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INTRODUCTION

While most individuals recover following traumatic stress exposures, a substantial subset develops adverse neurobiological outcomes, the most common of which is chronic posttraumatic musculoskeletal pain (CPMP).[1]

Consistent with other types of pain, CPMP is more common in women than in men, suggesting different risk/resiliency factors predicting CPMP development and different mechanisms driving the transition from acute to chronic pain.[2]

One such promising resiliency factor/mediator of CPMP is 17β-estradiol (E2). E2 is the main female sex-hormone in reproductive aged women and has been shown to have both pro- and anti- nociceptive effects.[3]

Previous evidence suggests that E2 might be a resiliency factor and/or protect against CPMP and related neuropsychiatric disorder development following trauma exposure.[4,5]

The current study assessed whether peritraumatic levels of E2 influence CPMP development in women following three common types of trauma exposure in industrialized nations, motor vehicle collision (MVC), sexual assault (SA), and major thermal burn injury (MThBI).

HYPOTHESIS

(1) Women with higher circulating levels of E2 at the time of trauma exposure develop less severe CPMP following trauma compared to women with lower circulating levels of E2.
(2) E2 levels influence the expression of RNA transcripts that mediate the development of CPMP following trauma exposure.

METHODS

Three different multiethnic longitudinal cohort studies of trauma survivors were utilized for the collection of relevant data. These cohorts enrolled individuals experiencing motor vehicle collision (MVC, n=89), sexual assault (n=64), and major thermal burn injury (MThBI, n=14).[6-8]

CPMP severity (MVC and SA) and graft site MSP severity (MThBI) in the past week was assessed in the immediate aftermath of trauma and at all three following timepoints at 6-weeks, 6-months, and 1-year, after trauma via a 0 (no MSP) to 10 (maximum MSP) numeric rating scale.

Blood samples were collected into EDTA and PAXgeneRNA tubes in the immediate aftermath of trauma exposure. Plasma was immediately separated via centrifugation and stored at -80°C and RNA PAXgene tubes were incubated at room temperature for 2 hours before freezing at -80°C. Blood plasma was thawed on ice immediately before 17β-estradiol analysis, which was performed in technical duplicate or triplicate using the Ultrasensitive Estradiol Enzyme-linked Immunosorbent Assay (ALPCO, Salem, NH, Catalog #20-ESTHUU-E01). RNA expression was measured via RNA-sequencing as previously described.[9]

Repeated measures mixed models were used to assess the relationship between log-transformed E2 levels and CPMP. Secondary analyses of MVC cohort RNA expression data (n=37) evaluated mediating transcripts ($p<0.05$) and associated biological pathways (Ingenuity, IPA, Qiagen). Statistical analyses were performed using SAS software v9.4 or R Studio v3.3.3.

TABLE 1 and FIGURE 1. Cohort characteristics and study design. Women from three longitudinal studies were included. All women were enrolled in the immediate aftermath of trauma. Blood plasma was collected and assayed for circulating 17β-estradiol (E2) levels.

Characteristic	
Participants, n	167
Age, years, mean (SD)	29.56 (9.67)
Ethnicity, n (%)	
Black	99 (59)
White	50 (29.9)
Multiethnic or Other	18 (10.7)
Education, n (%)	
HS or less	50 (30)
Some college	77 (46)
College or higher	37 (22)
BMI, mean (SD)	28.97 (8.31)
Pain sev in ED/ SANE, mean (SD)	6.12 (2.54)
Previous traumatic events, mean (SD)	3.75 (3.07)

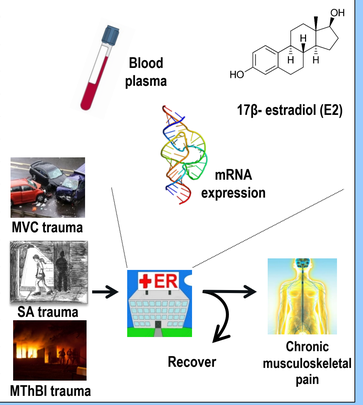


FIGURE 3. Women with high circulating levels of 17β-estradiol at the time of motor vehicle collision (left, n=89), sexual assault (middle, n=64), and thermal burn injury (right, n=14)

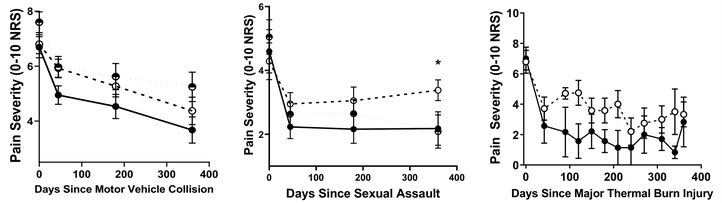


FIGURE 4. Secondary analyses assessing potential biological pathways that mediate the relationship between E2 and chronic pain severity identified

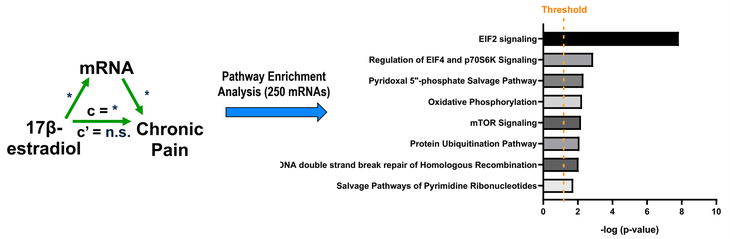
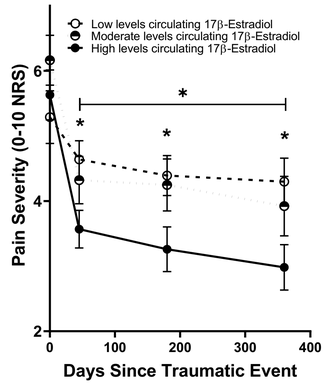


TABLE 2. Peritraumatic 17β-estradiol levels predict persistent pain severity in women following trauma (n=167)

	β	S.E.	p value
Intercept	4.167	1.485	0.010
Time	-0.059	0.037	0.191
17β-estradiol	-0.353	0.164	0.033
Age	0.031	0.021	0.145
BMI	0.004	0.025	0.861
Education 1	-0.040	0.456	0.930
Education 2	-0.142	0.553	0.797

FIGURE 2. Women with high circulating levels of 17β-estradiol at the time of trauma exposure report lower pain severity in the subsequent days and weeks (n=167). 17β-estradiol levels were measured in blood plasma collected within 24 hours of motor vehicle collision, sexual assault, and thermal burn injury. Pain levels were assessed (0-10 numeric rating scale) at the time of blood plasma collection (day 0) and at three additional timepoints over the course of a year (six weeks, six months, one year). Closed black circles = high 17β-estradiol levels (>100 pg/ml), partially shaded circles = moderate 17β-estradiol levels (30-100 pg/ml), and open circles = low 17β-estradiol levels (<30 pg/ml). Error bars represent standard error of the mean. *p<0.05



RESULTS

- Characteristics of the study sample are shown in Table 1. All participants were women and the majority were African American/Black. Most were less than 40 years old, had some college education, and were overweight (average BMI = 29).
- An inverse relationship between peritraumatic E2 and the development of CPMP was observed (β=-0.353, p=0.033) such that women with high E2 at the time of trauma had less CPMP over the following year.
- Secondary analyses identified 250 mRNA that mediated the relationship between E2 and CPMP; initial enrichment analyses identified eIF2 signaling as a top pathway through which E2 might influence CPMP development.

CONCLUSIONS

We show that increased peritraumatic E2 levels predict improved CPMP outcomes in women. This relationship might be mediated by E2 regulation of pain-associated RNA transcripts. Further studies are needed to validate this finding.

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