Opioid receptor gene expression differentially predicts chronic posttraumatic pain in women and men

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INTRODUCTION

Traumatic events are common in life. While most individuals recover following trauma exposure, a substantial proportion develop chronic posttraumatic pain (CPTP)[1]. Consistent with data from other types of pain conditions, women are at greater risk of CPTP than men[2].

Previous studies suggest that the relationship between the endogenous opioid response following trauma/stress exposure and CPTP development may differ in women vs. men[3,4].

In the current prospective observational study we evaluated for potential sex differences in the relationship between CPTP development and peritraumatic opioid receptor expression (*OPRM1, OPRD1, OPRK1*) in women and men following one of the most common types of trauma exposure in industrialized nations, motor vehicle collision (MVC).

In secondary analyses, based on previous studies demonstrating that opioid receptor binding can be influenced by sex hormones[5,6], we explored the relationship between opioid receptor expression and circulating 17β-estradiol levels.

METHODS

Cohort - African American (AA) individuals ≥ 18 and ≤ 65 years of age presenting to one of ten emergency departments (EDs) within 24 hours of MVC who did not have fracture or require hospital admission were enrolled. In this longitudinal study, CPTP severity (0-10 NRS) was assessed 6 weeks, 6 months, and 1 year following MVC. Exogenous opioid use in the week prior to each follow-up time point was also assessed.

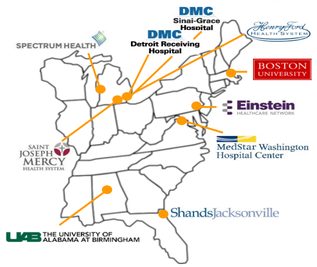
RNA collection and analysis - Blood was collected in the ED using PAXgene RNA tubes (n = 184) and stored at -80°C until use. Total RNA was prepared for sequencing using Ovation Human Blood RNA seq kits (NuGen). Sample libraries were sequenced on a HiSeq2500 system (Illumina). Raw sequencing reads were aligned to hg19 using STAR, quantified using RSEM, and normalized to the overall upper quartile.

17β-estradiol collection and analysis – Blood was collected in the ED using EDTA tubes (n=95) and plasma was separated via centrifugation. Plasma 17β-estradiol levels were measured using Ultrasensitive Estradiol ELISA kits (Alpco). For statistical analyses, women were grouped into high, medium, and low levels of 17β-estradiol based on tertiles or into high or low levels based on median circulating levels.

Statistics - The association between *OPRM1, OPRD1,* and *OPRK1* mRNA expression levels and post-MVC CPTP development was assessed using repeated measures mixed models adjusted for age, ED study site, and exogenous opioid use. The relationship between 17β-estradiol and *OPRM1* mRNA expression levels was assessed via an interaction term in the model (adjusted for age and ED study site).

TABLE 1 and FIGURE 1. Participants, enrollment sites, and study design

Characteristic	
Participants, n	184
Females, n (%)	120 (65)
Age, years, mean (SD)	31 (10)
Education, n (%)	
High school or less	66 (36)
Some college	75 (41)
College	29 (16)
Post-college	7 (4)
Exogenous opioid use wk 6, n (%)	30 (17)



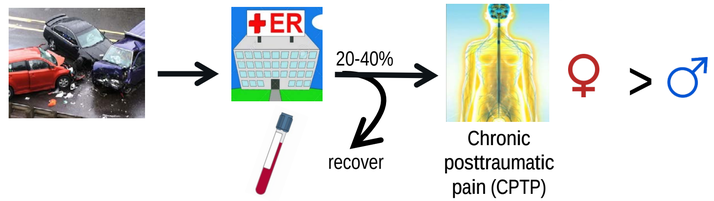
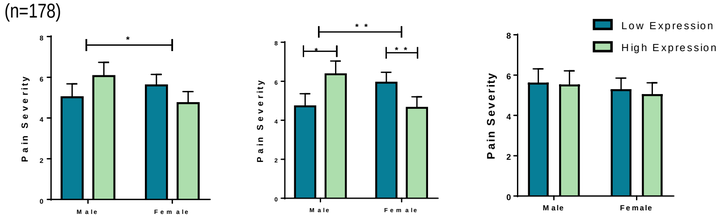


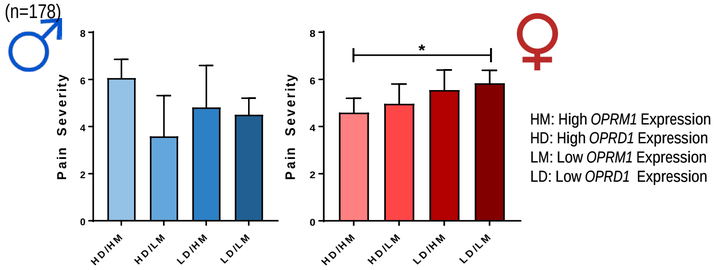
FIGURE 2. Peritraumatic mRNA expression levels of *OPRM1* (panel a) and *OPRD1* (panel b), but not *OPRK1* (panel c) differentially predict CPTP severity in men and women following MVC. Women with high expression levels of *OPRM1* or *OPRD1* reported less CPTP following MVC while men with high expression levels of these mRNA reported increased CPTP. * p<0.05 **p<0.01. (n=178)



a. *OPRM1* b. *OPRD1* c. *OPRK1*

*included only individuals with the major allele at the common A118G variant (>95% individuals)

FIGURE 3. A significant interaction was observed between *OPRM1* and *OPRD1* mRNA expression levels, such that in women, high levels of expression of both opioid receptors conveyed the least CPTP severity while low levels of expression of both opioid receptors was associated with the most CPTP severity. This same trend was not observed in men. * p<0.05, (n=178)



HM: High *OPRM1* Expression
HD: High *OPRD1* Expression
LM: Low *OPRM1* Expression
LD: Low *OPRD1* Expression

FIGURE 4. Women with high circulating levels of 17β-estradiol report less severe CPTP 6 weeks and 1 year following MVC than women with low or median circulating levels of 17β–estradiol. *p<0.05 (n=95)

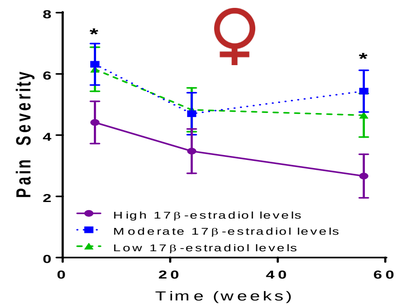
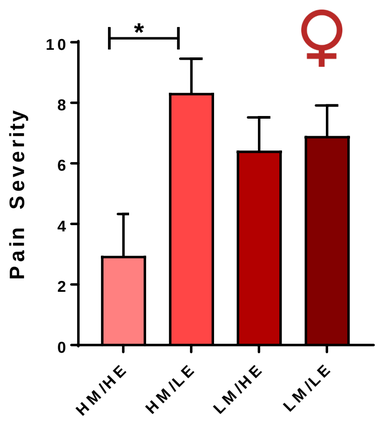


FIGURE 5. The relationship between circulating 17β–estradiol and opioid receptor expression levels influences CPTP severity six weeks following MVC. A significant interaction was observed for 17β–estradiol x *OPRM1* mRNA expression such that women with high levels of both *OPRM1* mRNA expression and high circulating levels of 17β–estradiol reported the lowest CPTP severity. A significant interaction was not observed for 17β–estradiol x *OPRD1*. * p<0.05, (n=38).



HM: High *OPRM1* Expression
HE: High Estradiol Expression
LM: Low *OPRM1* Expression
LE: Low Estradiol Expression

RESULTS

mRNA and plasma samples were obtained from study participants enrolled following MVC at 10 US Emergency Department sites across the Eastern US (Figure 1). All individuals were African American and between the ages of 18-65 (Table 1).

A significant interaction between participant sex and *OPRM1, OPRD1* mRNA expression levels was observed (p = 0.039 and 0.001, respectively). In women, high expression levels of either of these opioid receptors was associated with low CPTP (Figure 2).

Women with high expression levels of both *OPRM1* and *OPRD1* mRNA report the least CPTP in the months following MVC (Figure 3).

Women with high circulating levels of 17β–estradiol in the early aftermath of MVC report the lowest CPTP severity 6 weeks and 1 year following MVC (Figure 4).

The lowest CPTP severity was reported by women with high levels of both *OPRM1* mRNA expression and 17β–estradiol (Figure 5).

CONCLUSIONS

The results of this study suggest that opioid receptor expression levels influence CPTP outcomes differently in men and women and that the sex hormone 17β–estradiol may influence opioid receptor levels and their effect on CPTP in women following MVC.

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