Psychoneuroendocrinology 69 (2016) 150–160

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Oxytocin receptor DNA methylation in postpartum depression

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ARTICLE INFO

Article history:
Received 23 September 2015
Received in revised form 7 April 2016
Accepted 7 April 2016

Keywords:
Postpartum depression
Trauma
DNA methylation
OXTR
Allopregnanolone
Estradiol

ABSTRACT

The oxytocin receptor (*OXTR*) is a key regulator of stress and anxiety and may be regulated by both psychosocial risk factors and gonadal hormones, making it an attractive candidate for study in postpartum depression (PPD). The objective of this study was to investigate both serum hormone and PPD specific DNA methylation variation in the *OXTR*. Illumina HM450 microarray data generated in a prospective PPD cohort identified significant associations (P = 0.014) with PPD in an intronic region in the *OXTR* located 4 bp proximal to an estrogen receptor (ER) binding region. Pyrosequencing confirmed moderate evidence for an interaction of CpGs in the region with childhood abuse status to mediate PPD. These CpGs located on chr3 at positions 8810078 and 8810069 exhibited significant associations with postpartum depression scores from an independent cohort of 240 women with no prior psychiatric history. Hormone analysis suggested a PPD specific negative correlation of DNA methylation in the region with serum estradiol levels. Estradiol levels and *OXTR* DNA methylation exhibited a significant interaction to associate with the ratio of allopregnanolone to progesterone. Cumulatively, the data corroborate our previous hypotheses of a PPD specific increased sensitivity of epigenetic reprogramming at estrogen target genes and suggests that *OXTR* epigenetic variation may be an important mediator of mood relevant neuroactive steroid production.

1. Introduction

Postpartum depression (PPD) affects between 10 and 20% of women (Josefsson et al., 2001; Miller, 2002; Pearlstein et al., 2009) and has significant adverse effects on both mother and child (Breese McCoy, 2011; Cuijpers et al., 2008; Field, 2011; Hirst and Moutier, 2010; O'Hara, 2009; Soufia et al., 2010). PPD afflicts some populations at even higher rates, for example, 30% of women with a history of depression and 52% of women with bipolar disorder (Viguera et al., 2011). A growing body of evidence indicates that an increased sensitivity to change in gonadal hormone levels may mediate a biological vulnerability to PPD, with much of the available evidence implicating the estrogens (Bloch et al., 2000; Guintivano et al., 2014; Mehta et al., 2014). Critically, it is not the levels of estrogens so much as differences in the downstream responses and physiological consequences to them that may confer risk onto vulnerable women.

Importantly, PPD has also been associated with differences in levels of other hormones, including corticotrophin releasing hormone (Magiakou et al., 1996), triiodothyronine (Bunevicius et al., 2009; Pedersen et al., 2007), testosterone (Aswathi et al., 2015), and oxytocin (Skrundz et al., 2011), among others. Some of these associations may represent the complex interplay between dysregulated hormone systems and their downstream consequences. Of particular interest are hormones linked with estrogen signaling including progesterone, its metabolites, and oxytocin.

Progesterone withdrawal and progesterone receptor antagonists lead to depressive phenotypes. Metabolites of progesterone in the brain, specifically allopregnanolone, modulate GABA(A) recep-

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http://dx.doi.org/10.1016/j.psyneuen.2016.04.008
0306-4530/

Table 1
Sample demographics.

Cohort	Johns Hopkins Prospective PPD Cohort	Prospective Gene Expression PPD Cohort	FRAMES cohort
Total	51	61	240
PPD: Antenatal Euthymic	10	1st:15; 3rd: 15	5
PPD: Antenatal Depressed	12	1st:14; 3rd: 18	0
No PPD: Antenatal Euthymic	22	1st:22; 3rd: 28	235
No PPD: Antenatal Depressed	7	0	0
PPD Assessment	Prospective Clinical	Prospective HDRS, BDI, EPDS[a]	Prospective HDRS
Age	30.68 ± 6.32	33	32.7 ± 0.018
1st trimester	9	51	0
2nd trimester	22	0	0
3rd trimester	20	61	0
Postpartum	0	0	240
% Caucasian: African American: Other	30:70:0%	85:15:0%	100:0:0%
Childhood Sexual Abuse	19	NA	NA
No Childhood Sexual Abuse	29	NA	NA
Procedures			
Illumina HM450 beadchip	51	0	0
OXTR Targeted Pyrosequencing	51	0	240
Illumina HumanHT-12 V4.0 expression beadchip	0	61	0
Hormone Analysis	31	0	0

[a] Depression diagnoses as reported by Mehta et al. (2014) for the various time points were based on satisfying all of the following criteria: 1st trimester: Hamilton Depression Rating Scale (HDRS) > 14, Edinburgh Postnatal Depression Scale (EPDS) > 12, Beck Depression Inventory (BDI) > 15; 3rd Trimester: HDRS > 15, EPDS > 15, BDI > 12; 3 months postpartum: HDRS > 14, EPDS > 11, BDI > 16.

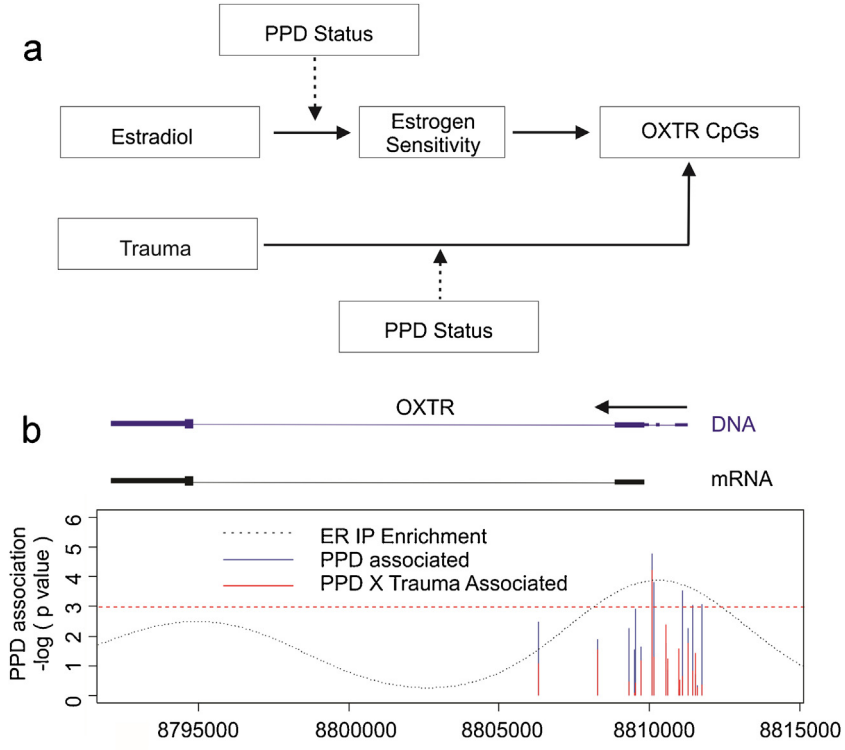

Fig. 1. Location of model associated *OXTR* DNA methylation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
(a) A schematic representation of the model being tested in the manuscript. Estrogen sensitivity was not directly tested in our models, but represents a hypothesized explanatory variable mediating the effects of estradiol on *OXTR* DNA methylation. (b) A plot of the nominal negative natural log of the p values for loci associated with postpartum depression (PPD) (y axis) as a function of genomic coordinates on chr 3 in the region of the *OXTR* gene (hg 19). Only those 7CpGs exhibiting significant Bonferroni corrected associations to the cg25140571 probe found in BrainCloud are depicted. The horizontal red dashed line denotes a p value of 5%. ENCODE data downloaded from Gene Expression Omnibus accession GSE32465 was used to evaluate empirically determined binding sites for ERα binding in ECC1 and T-47D cells. Data was downloaded from Gene Expression Omnibus accession GSE32465 and the frequency of sequences aligning to genomic coordinates following chromatin immunoprecipitation with antibodies for estrogen receptor alpha (ERα) are depicted by the dotted black line. A schematic of the genomic DNA *OXTR* gene as depicted on the UCSC genome browser (https://genome.ucsc.edu/) (blue) and mRNA for splice variant E05109 (black) is depicted to scale with the horizontal black arrow denoting the direction of transcription.

tors in a concentration dependent manner, resulting in sedation and anxiolytic effects in some cases and anxiogenic, aggressive, and irritable effects in others (Andreen et al., 2009; Backstrom et al., 2011; Studd, 2011). Levels of allopregnanolone may also be closely tied to estradiol signaling, as estradiol administration to ovariectomized (OVX) rats restored deficits in both this progesterone metabolite and beta-endorphin (Yim et al., 2010) and resulted in anxiolytic effects in another progesterone withdrawal model rat (Windle et al., 2006).