Hormones and Behavior 96 (2017) 84–94

Contents lists available at ScienceDirect

Hormones and Behavior

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

Perinatal depression and DNA methylation of oxytocin-related genes: a study of mothers and their children

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ARTICLE INFO

Keywords:
Perinatal depression
Mother-child dyads
Epigenetics
DNA methylation
Oxytocin receptor
Intergenic region

ABSTRACT

The present study investigated the association of perinatal depression (PD) with differential methylation of 3 genomic regions among mother and child dyads: exon 3 within the oxytocin receptor (OXTR) gene and 2 intergenic regions (IGR) between the oxytocin (OXT) and vasopressin (AVP) genes. Maternal PD was assessed at 5 time-points during pregnancy and postpartum. Four groups were established based on Edinburgh Postnatal Depression Scale (EPDS) cut-off scores: no PD, prenatal or postpartum depressive symptoms only and persistent PD (depressive symptoms both prenatally and postpartum). Salivary DNA was collected from mothers and children at the final time-point, 2.9 years postpartum. Mothers with persistent PD had significantly higher overall OXTR methylation than the other groups and this pattern extended to 16/22 individual CpG sites. For the IGR, only the region closer to the AVP gene (AVP IGR) showed significant differential methylation, with the persistent PD group displaying the lowest levels of methylation overall, but not for individual CpG sites. These results suggest that transient episodes of depression may not be associated with OXTR hypermethylation. Validation studies need to confirm the downstream biological effects of AVP IGR hypomethylation as it relates to persistent PD. Differential methylation of the OXTR and IGR regions was not observed among children exposed to maternal PD. The consequences of OXTR hypermethylation and AVP IGR hypomethylation found in mothers with persistent PDS may not only impact the OXT system, but may also compromise maternal behavior, potentially resulting in negative outcomes for the developing child.

1. Introduction

Early life stress (ELS) can impact neural, cognitive and affective functioning, potentially exerting long-lasting effects on the brain and behavior (Kaufman, Plotsky, Nemeroff, & Charney, 2000; Labonte et al., 2012). The enduring effects of ELS are likely due to the fact that early life is a critical period for brain development, making the nervous system particularly receptive to incoming signals from its environment thereby "programming" neural pathways in response to these signals (Reynolds, Labad, Buss, Ghaemmaghami, & Raikkonen, 2013; Stiles & Jernigan, 2010). Since early life can include the period in utero as well as the postpartum period, the maternal environment, both in utero and postpartum, has been implicated as one of the factors shaping early life experience. For this reason, perinatal depression (PD) has been the subject of emerging research in the field of ELS and vulnerability to disease. PD encompasses major and minor depressive episodes during pregnancy and up to 1 year after delivery (Gavin et al., 2005). PD affects up to 18–19% of women (Gavin et al., 2005) and contributes to poorer maternal care in the postnatal period. Specifically, depressed mothers exhibit reduced maternal sensitivity, responsiveness and attachment. As a result, they may have trouble bonding with their child, soothing them or responding to their needs (Campbell, Matestic, von Stauffenberg, Mohan, & Kirchner, 2007; Field, 2010; Perry, Ettinger, Mendelson, & Le, 2011).

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http://dx.doi.org/10.1016/j.yhbeh.2017.09.006
Received 20 March 2017; Received in revised form 8 August 2017; Accepted 12 September 2017

Due to the impact of PD on maternal care, combined with the potential long-term effects of PD on the growing fetus (Rifkin-Graboi et al., 2013), PD has been identified as a risk factor for behavioral problems in children, including conduct disorders as well as learning difficulties and impaired emotional regulation (Narayanan & Naerde, 2016; Sirvinskiene, Zemaitiene, Jusiene, & Markuniene, 2016). Moreover, PD may contribute to poorer immune function, increased sensitivity to stress later in life and higher risk for psychopathology in the developing child (Babenko, Kovalchuk, & Metz, 2015; Essex, Klein, Cho, & Kalin, 2002; Sapolsky, 2004). Given these implications, a better understanding of the biological mechanisms underlying PD may be useful in the development of new treatment avenues and tools for prevention.

1.1. Oxytocin

The oxytocin (OXT) system has been proposed as one mechanism altered in depression (Kirsch, 2015) due to its role in stress regulation. OXT is a neuropeptide and hormone that has been shown to dampen hypothalamic-pituitary-adrenal (HPA) axis over-activity by reducing excess cortisol (Bisagno & Cadet, 2014). OXT has anxiolytic properties in part because it reduces stress, but also because it increases the salience of pro-social cues thereby facilitating trust, bonding, social support seeking, empathy, attachment and social cognition (Heinrichs, von Dawans, & Domes, 2009; Seltzer, Ziegler, Connolly, Prososki, & Pollak, 2014). OXT also stimulates lactation as well as uterine contractions and is associated with maternal behavior (Carson, Guastella, Taylor, & McGregor, 2013), enabling mothers to be more attuned and sensitive to their infants' cues (Feldman, Weller, Zagoory-Sharon, & Levine, 2007; Kim, Fonagy, Koos, Dorsett, & Strathearn, 2014). There remains some inconsistency in findings about how circulating OXT levels are associated with psychological and social functioning (Garfield, Mathews, & Janusek, 2015) although the majority of studies have found that lower levels of plasma OXT were associated with depression, autism and anorexia nervosa (Maguire, O'Dell, Touyz, & Russell, 2013; Modahl et al., 1998; Scantamburlo et al., 2007). Still, a recent meta-analysis revealed that there were no substantial differences in peripheral OXT levels between psychiatric patients and healthy controls (Rutigliano et al., 2016). These inconsistencies could be due to the fact that OXT levels tend to vary throughout the day and according to where a woman is in her menstrual cycle (Acevedo-Rodriguez, Mani, & Handa, 2015; Huber, Veinante, & Stoop, 2005). Also, methodological issues such as whether samples are extracted or not heavily influence how circulating OXT is detected and measured (Bachner-Melman & Ebstein, 2014). Taken together, measures of peripheral OXT are highly variable, making it necessary to explore other aspects of the OXT system that are likely to influence OXT function, as well as other biomarkers that are relatively more stable and reliable (Auger & Auger, 2013).

Epigenetic regulation can provide insight into the mechanisms underlying gene-environment interactions. Epigenetics is a molecular process that regulates gene function without modifying the underlying genetic sequence (Lester, Conradt, & Marsit, 2016). This adaptable feature allows the genome (and the organism) to prepare for various environmental conditions and some of these adaptations may be long-term (Szyf, 2013). There are several known epigenetic mechanisms (Marsit, 2015) although DNA methylation is the most studied epigenetic modification to date (Dalton, Kolshus, & McLoughlin, 2014). Typically, methylation refers to the addition of a methyl group to a cytosine in the context of a CpG site in the genome (Bird, 1986; Holliday, 1989) although non-CpG methylation has been characterized (Pietrzak, Rempala, Nelson, & Hetman, 2016; Ramsahoye et al., 2000). These methyl groups can block transcription factors from binding to the gene or attract methylation-binding proteins, thereby altering gene expression (Jin et al., 2016). However, transcription factors as readers of DNA methylation have also been reported (Zhu, Wang, & Qian, 2016).

The majority of human OXTR methylation studies focus on the association between methylation of the OXTR gene and psychopathology; namely depression (Chagnon, Potvin, Hudon, & Preville, 2015; Reiner et al., 2015; Simons, Lei, Beach, Cutrona, & Philibert, 2016), anorexia nervosa (Kim, Kim, Kim, & Treasure, 2014), autism (Gregory et al., 2009; Rijlaarsdam et al., 2016; Yuksel, Yuceturk, Karatas, Ozen, & Dogangun, 2016), social anxiety (Ziegler et al., 2015) and callous-unemotional traits in children with conduct disorders (Cecil et al., 2014; Dadds et al., 2014). Although a few studies have examined OXTR methylation in relation to postpartum depression (Bell et al., 2015; Kimmel et al., 2016) and prenatal depression (Unternaehrer et al., 2016), none have investigated OXTR methylation with respect to depression experienced over the entire perinatal period. The two studies assessing OXTR methylation and postpartum depression found that increased methylation of CpG site −934 was only associated with the occurrence of postpartum depression if participants also possessed an A-allele for the rs53576 SNP (Bell et al., 2015) while the other study discovered that postpartum depression was linked to decreased methylation, but independent of genotype and at two different CpG sites (Kimmel et al., 2016). A third study examining prenatal depression and overall OXTR methylation within exon 3, found that depressive symptoms predicted decreased methylation (Unternaehrer et al., 2016).

1.2. Vasopressin

Arginine vasopressin (AVP) is another neuropeptide that is implicated in maternal behavior (particularly maternal aggression) and stress regulation (Bachner-Melman & Ebstein, 2014; Bridges, 2014). However, unlike OXT which is anxiolytic, AVP is anxiogenic because it stimulates rather than suppresses HPA axis activity (Heinrichs et al., 2009; Stoop, 2012). In circumstances of acute stress, AVP contributes to adrenocorticotropic hormone (ACTH) release while for chronic stress, AVP supercedes corticotropin-releasing hormone (CRH) activation in response to HPA axis regulation (Aguilera, Subburaju, Young, & Chen, 2008; Rotondo et al., 2016). Due to OXT and AVP's similarity in chemical structure and function, it has been theorized that they co-evolved and derived from a common ancestral gene (Gimpl & Fahrenholz, 2001). For example, the AVP and OXT genes are located on the same chromosome (chromosome 3), are adjacent to each other and share a relatively small intergenic region (IGR). Although the significance of the AVP/OXT IGR has been documented in animal studies, there are no studies to date that have investigated methylation of the AVP/OXT IGR in humans. Animal studies not only confirm that methylation of the AVP/OXT IGR and AVP gene expression are negatively correlated, but that this region is differentially methylated by the early life environment (Murgatroyd & Spengler, 2014) and that ELS is linked to IGR hypomethylation in hypothalamic neurons (Murgatroyd et al., 2009). One human study assessed methylation of the OXT promoter region and found that lower OXT methylation was related to secure attachment and better social cognition (Haas et al., 2016). However, according to the IGR hypothesis, enhancers corresponding to OXT and AVP gene expression are not present in the promoter or upstream regions of these genes, but are rather located in the IGR downstream of the AVP gene (Gainer, Fields, & House, 2001). Therefore, given that the downstream molecular function of the AVP/OXT IGR has been verified in rodent models (and contains sequences that are relatively conserved in humans), this genomic region makes for a more promising candidate.

1.3. The current study

Accordingly, three genomic regions have been chosen for further investigation: exon 3 within the OXT receptor (OXTR) gene (Fig. 1, diagram A) and two intergenic regions (IGR) between the OXT and vasopressin (AVP) genes. This AVP/OXT IGR spans ~10 kb and is located on chromosome 20 (Fig. 1, diagrams B and C). The goal of the current study was to assess methylation patterns of certain regulatory