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Oxytocin pathways in the intergenerational transmission of maternal early life stress

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ABSTRACT

Severe stress in early life, such as childhood abuse and neglect, constitutes a major risk factor in the etiology of psychiatric disorders and somatic diseases. Importantly, these long-term effects may impact the next generation. The intergenerational transmission of maternal early life stress (ELS) may occur via pre-and postnatal pathways, such as alterations in maternal-fetal-placental stress physiology, maternal depression during pregnancy and postpartum, as well as impaired mother-offspring interactions. The neuropeptide *oxytocin* (OT) has gained considerable attention for its role in modulating all of these assumed transmission pathways. Moreover, central and peripheral OT signaling pathways are highly sensitive to environmental exposures and may be compromised by ELS with implications for these putative transmission mechanisms. Together, these data suggest that OT pathways play an important role in the intergenerational transmission of maternal ELS in humans. By integrating recent studies on gene-environment interactions and epigenetic modifications in OT pathway genes, the present review aims to develop a conceptual framework of intergenerational transmission of maternal ELS that emphasizes the role of OT.

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Abbreviations: 5HTTLPR, Serotonin Transporter Length Polymorphic Region; BPD, Borderline Personality Disorder; CNS, Central Nervous System; CpG, Cytosine-Guanine DNA Sequence; CRH, Corticotropin Releasing Hormone; CSF, Cerebrospinal Fluid; DA, Dopamine; *DAT*1, Dopamine Transporter Gene 1; DNA, Deoxyribonucleic Acid; *DRD*2, *DRD*4, Dopamine Receptor 2 and Dopamine Receptor 4 Genes; E, Estrogens; ELS, Early Life Stress; GABA, Gamma Amino Butric Acid; HPA, Hypothalamic Pituitary Adrenal Axis; i.c.v., Intracerebroventricular; IL-1β, Interleukin 1 beta; IL-6, Interleukin 6; LG, Licking and Grooming; MDD, Major Depressive Disorder; MPF, Maternal-Placental-Fetal; MPOA, Medial Preoptic Area; mRNA, Messenger Ribonucleic Acid; nAcc, Nucleus Accumbens; OT, Oxytocin; OTR, Oxytocin Receptor; *OXTR*, Oxytocin Receptor Gene (human); *Oxtr*, Oxytocin Receptor Gene (rodents); PPD, Postpartum Depression; PVN, Paraventricular Nucleus; Rs, Reference Number for Single Nucleotide Polymorphism (e.g., rs53576); SNP, Single Nucleotide Polymorphism; TNF-α, Tumor Necrosis Factor alpha; ToM, Theory of Mind; VMN, Ventromedial Nucleus; VS, Ventral Striatum; VTA, Ventral Tegmental Area.

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1. Introduction

It is well-established that the exposure to one or multiple forms of early-life stress (ELS), like childhood abuse and neglect, constitutes a major risk factor in the etiology of a wide range of somatic and/or psychiatric diseases (Anda et al., 2006; Felitti et al., 1998; Heim and Binder, 2012). However, it becomes increasingly apparent that these adverse long-term consequences are not restricted to the exposed individual alone but might be transmitted to the next generation (Collishaw et al., 2007), who also are at increased risk for psychiatric and somatic disorders (Roberts et al., 2014; Roberts et al., 2013) – a phenomenon referred to as *intergenerational transmission* (Bowers and Yehuda, 2016). Most studies discuss postnatal transmission pathways, such as non-optimal parenting behavior and psychopathology in ELS-exposed parents (Miranda et al., 2013) and offspring victimization (Plant et al., 2013). It is important to acknowledge however, that postnatal behavioral pathways, like postpartum depression and/or altered maternal behavior, are already primed during pregnancy (Feldman et al., 2007; Skrundz et al., 2011). Moreover, initial empirical evidence reveals ELS-associated alterations in maternal-fetal-placental (MPF) stress physiology that have been shown to alter fetal developmental trajectories (Moog et al., 2015). We therefore propose a continuous intergenerational transmission of maternal ELS that likely occurs during both the pre- and postnatal period via ELS-associated alterations in stress-sensitive biological systems, which may affect fetal development as well as the quality of postnatal dyadic mother-child interactions.

Within this context, we want to emphasize the role of the neuropeptide oxytocin (OT) as a key neuroendocrine factor modulating these candidate pre- and postnatal transmission pathways of maternal ELS. OT has gained considerable attention in studies of human social behaviors (Lee et al., 2009), including parenting (Bakermans-Kranenburg and van Ijzendoorn, 2008; Gordon et al., 2010; Lee et al., 2009; Meyer-Lindenberg et al., 2011) and attachment formation (Levine et al., 2007). Interestingly, there is evidence that ELS is associated with lower OT concentrations in the cerebrospinal fluid (CSF) of adult women (Heim et al., 2009) and non-human primates (Winslow et al., 2003). This ELS-induced reduction in CSF-OT was linked to pronounced deficiencies in social behavior in the study by Winslow et al. (2003). This suggests that central availability and functioning of the OT system may be susceptible to environmental factors such as ELS, which persist into adulthood and may impact functional integrity of the "parental brain". It is also suggested that OT may play an important role in the development of depression (McQuaid et al., 2014), which is a highly prevalent clinical consequence of ELS and a condition that may interfere with optimal parenting behavior (Beck, 1995; Feldman, 2015b; Field, 2010). Finally, OT modulates the activity of stress-sensitive biological systems, such as the HPA-axis (Cardoso et al., 2014) and the immune system (Wang et al., 2015), which have been previously proposed to affect fetal development (Entringer et al., 2015). Taken together, these findings suggest OT signaling to be an exquisite target for pre- and postnatal pathways of intergenerational transmission of maternal ELS, which is further substantiated by findings in rodents (Champagne, 2008).

For the identification of putative OT pathways in the intergenerational transmission of maternal ELS in humans, it is important to gain a better understanding of 1) the function of OT in central and peripheral mechanisms that act as likely transmission pathways (e.g., altered MPF stress physiology, depression, parenting behavior), 2) the mechanisms that explain *how* ELS exposure affects OT signaling and thereby influences physiological stress regulation, depression risk and parenting behavior, 3) individual (genetic) differences that confer higher risk or resilience to the effects of ELS on OT-dependent phenotypes, and 4) when and how the effects of maternal ELS are transmitted to the next generation to alter offspring developmental trajectories. Recent studies are beginning to address some of these questions by focusing on epigenetic modifications and common genetic variants in OT-pathway genes (i.e., genes that either code for the peptide and/or its receptor) that may interact with environmental factors (e.g., ELS) to account for phenotypic variability, such as risk for emotional dysregulation, insecure attachment, depression, or anxiety symptoms (Bradley et al., 2011; McQuaid et al., 2013; Thompson et al., 2011). In particular, sequence variations and epigenetic modifications in the oxytocin receptor gene have emerged as promising candidates in numerous studies and will therefore receive of particular attention in this review. Finally, the aim of the present work is to integrate relevant findings in order to elaborate a theoretical framework of oxytocin pathways in the intergenerational transmission of maternal ELS, which is shown in Fig. 1.

2. OT and early-life stress (ELS) – role in shaping neural circuits that underlie parenting behavior and depression risk

2.1. Oxytocin (OT) and the oxytocin receptor (OTR)

OT is a small nonapeptide which is highly conserved among mammalian species (Donaldson and Young, 2008). The OT gene, which first codes for a preprohormone that is then processed to