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Maternal PTSD associates with greater glucocorticoid sensitivity in offspring of Holocaust survivors

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Summary Intergenerational effects of trauma have been observed clinically in a wide range of populations, and parental PTSD has been associated with an increased risk for psychopathology in offspring. In studies of Holocaust survivor offspring, parental PTSD, and particularly maternal PTSD, has been associated with increased risk for PTSD, low basal urinary cortisol excretion and enhanced cortisol suppression in response to dexamethasone. Such findings implicate maternally derived glucocorticoid programming in the intergenerational transmission of trauma-related consequences, potentially resulting from in utero influences or early life experiences. This study investigated the relative influence of Holocaust exposure and PTSD in mothers and fathers on glucocorticoid sensitivity in offspring. Eighty Holocaust offspring and 15 offspring of non-exposed Jewish parents completed evaluations and provided blood and urine samples. Glucocorticoid sensitivity was evaluated using the lysozyme suppression test (LST), an in vitro measure of glucocorticoid receptor sensitivity in a peripheral tissue, the dexamethasone suppression test (DST), and 24-h urinary cortisol excretion. Maternal PTSD was associated with greater glucocorticoid sensitivity in offspring across all three measures of glucocorticoid function. An interaction of maternal and paternal PTSD on the DST and 24-h urinary cortisol showed an effect of decreased glucocorticoid sensitivity in offspring with paternal, but not maternal, PTSD. Although indirect, these findings are consistent with the hypothesis that epigenetic programming may be involved in the intergenerational transmission of trauma-related effects on glucocorticoid regulation.
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The intergenerational transmission of the effects of trauma from survivors to their children has been observed primarily in populations in which the first generation was exposed to chronic and severe threat and horror such as occurred during the Holocaust, the Cambodian Khmer Rouge genocide, and the Israeli occupation of Gaza and the West Bank (Yehuda et al., 1998a; Field et al., 2011; Palosaari et al., 2013). Transmission to offspring of trauma-related consequences or vulnerability following a single, acute trauma has also been noted (Yehuda et al., 2005; Chemtob et al., 2010). Parental posttraumatic stress disorder (PTSD) appears to be a salient factor in the transmission of at least some of these effects (Yehuda et al., 1998b, 2001a; Leen-Feldner et al., 2013). For example, the presence of PTSD in Holocaust-exposed parents is associated with lower urinary cortisol excretion in non-exposed offspring (Yehuda et al., 2000, 2002a). Parental PTSD and associated symptoms may affect caregiving behavior which shapes the early "environment" of the offspring (Yehuda et al., 2001b; Zerach et al., 2012). Alternatively, it is possible that genetic risk factors that interact with trauma exposure to produce PTSD may be transmitted to offspring (Binder et al., 2008). In the former circumstance, maternal and paternal PTSD might have different effects on offspring as a result of distinct roles and involvement in childrearing. This would explain the previously observed finding that maternal, but not paternal, PTSD was associated with Holocaust offspring PTSD (Yehuda et al., 2008). Lower levels of cortisol have also been observed, primarily in relation to maternal PTSD (Yehuda et al., 2007b). Further, maternal psychopathology and early adverse experiences have been associated with glucocorticoid alterations (e.g., Essex et al., 2011; Azak et al., 2013).

Taken together, these findings raise the possibility of underlying maternally derived epigenetic mechanisms. Such mechanisms are also suggested by findings from a cohort of babies born to mothers exposed to the 9/11 terrorist attacks during pregnancy. Low salivary cortisol was observed in babies of mothers who developed PTSD following exposure in the 2nd or 3rd trimester (Yehuda et al., 2005). Ostensibly, these mothers "transmitted" a tendency for low cortisol levels via in utero glucocorticoid programming. Importantly, the pattern of low cortisol and increased HPA axis sensitivity noted in prior studies of offspring is similar to that observed in individuals with PTSD (Yehuda et al., 2002b, 2004; de Kloet et al., 2006; Morris et al., 2012), and has been associated with increased risk for the development of PTSD in a recent, prospective study in a large military sample (van Zuiden et al., 2012).

While the influences of maternal behavior on offspring stress responsivity have been extensively studied in animal models (Champagne and Meaney, 2006; Mychasiuk et al., 2011), recent investigations also show paternal influences on offspring biology, leading to an increased interest in the differential impacts of maternal and paternal stress and PTSD-like behaviors on offspring in animal studies (e.g., Mills-Koonce et al., 2011; Mychasiuk et al., 2013). For example, paternal exposure to chronic variable stress in both adolescent and adult mice was associated with changes in sperm microRNA content resulting in reduced, rather than enhanced, HPA axis responsivity in offspring (Rodgers et al., 2013). Interestingly, chronic social defeat stress in male rats resulted in increased anxiety- and depression-like behavioral phenotypes and basal corticosterone levels in the offspring. However, in vitro fertilization experiments showed that this model of transgenerational transmission may not only involve the sperm (Dietz et al., 2011). Early postnatal and adult paternal stress in rats has also been shown to affect offspring behavioral stress responses and DNA methylation patterns in brain tissue (Franklin et al., 2010; Mychasiuk et al., 2013). Understanding the mechanisms underlying the transmission of vulnerability from parent to child has important implications for the prevention and treatment of stress- and anxiety-related disorders.

The lysosome suppression test (LST) was developed to provide an in vitro measure of glucocorticoid receptor sensitivity in a peripheral tissue (Yehuda et al., 2003). The most widely used clinical test of glucocorticoid sensitivity, the dexamethasone suppression test (DST), measures the strength of negative feedback inhibition in the HPA axis following the oral ingestion of dexamethasone (DEX). However, as with any measure, the DST has some limitations. For example, the test is affected by the bioavailability of DEX (Guthrie, 1991), and depends on subject compliance with DEX ingestion (usually at home at a specific time) and timely arrival for blood drawing procedures 9 h following ingestion. Furthermore, in non-clinical populations there can be a reluctance to ingest a "steroid" analog.

Because glucocorticoids inhibit lysozyme activity, an in vitro administration of graded concentrations of DEX to peripheral blood mononuclear cells (PBMCs) can directly measure glucocorticoid responsiveness (i.e., the concentration at which lysozyme activity is diminished by 50%, or the $IC_{50\text{-}DEX}$ value). $IC_{50\text{-}DEX}$ has been robustly correlated with cortisol suppression as assessed by the DST (Yehuda et al., 2003), and lower $IC_{50\text{-}DEX}$ values, indicating increased sensitivity, have been associated with PTSD in veterans (Yehuda et al., 2004). Enhanced sensitivity on the $IC_{50\text{-}DEX}$ has also been associated with younger age of first trauma, indicating responsiveness to early environmental experiences (Yehuda et al., 2004).

The current study was designed to examine maternal versus paternal influences on glucocorticoid sensitivity in Holocaust offspring as assessed by the LST. Previous work with this population demonstrated an association between parental PTSD and enhanced glucocorticoid sensitivity demonstrated by the DST, indicating that offspring of Holocaust survivors with PTSD had greater cortisol suppression to DEX compared with demographically comparable controls (Yehuda et al., 2007a). It was hypothesized that maternal PTSD would exert a stronger influence on offspring glucocorticoid sensitivity than paternal PTSD, and that maternal PTSD would associate with higher sensitivity in offspring. Because concurrent offspring symptomatology (i.e., anxiety and depression) can be related to HPA axis functioning, the influence of these symptoms on the results was examined. Finally, the role of childhood family environment (as retrospectively reported by offspring) on glucocorticoid sensitivity was evaluated to determine whether such factors account for the effects of parental PTSD.

1. Methods

1.1. Participants

The study was approved by the Institutional Review Board of the Mount Sinai School of Medicine (MSSM), and all subjects