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Elevation of 11β-hydroxysteroid dehydrogenase type 2 activity in Holocaust survivor offspring: Evidence for an intergenerational effect of maternal trauma exposure

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Summary
Background: Adult offspring of Holocaust survivors comprise an informative cohort in which to study intergenerational transmission of the effects of trauma exposure. Lower cortisol and enhanced glucocorticoid sensitivity have been previously demonstrated in Holocaust survivors with PTSD, and in offspring of Holocaust survivors in association with maternal PTSD. In other work, reduction in the activity of the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD-2), which inactivates cortisol, was identified in Holocaust survivors in comparison to age-matched, unexposed Jewish controls. Therefore, we investigated glucocorticoid metabolism in offspring of Holocaust survivors to evaluate if similar enzymatic decrements would be observed that might help to explain glucocorticoid alterations previously shown for Holocaust offspring.
Methods: Holocaust offspring ($n = 85$) and comparison subjects ($n = 27$) were evaluated with clinical diagnostic interview and self-rating scales, and asked to collect a 24-h urine sample from which concentrations of cortisol and glucocorticoid metabolites were assayed by GCMS. 11β-HSD-2 activity was determined as the ratio of urinary cortisone to cortisol.
Results: Significantly reduced cortisol excretion was observed in Holocaust offspring compared to controls ($p = .046$), as had been shown for Holocaust survivors. However, 11β-HSD-2 activity

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was elevated for offspring compared to controls ($p = .008$), particularly among those whose mothers had been children, rather than adolescents or adults, during World War II ($p = .032$). The effect of paternal Holocaust exposure could not be reliably investigated in the current sample.
Conclusions: The inverse association of offspring 11β-HSD-2 activity with maternal age at Holocaust exposure is consistent with the influence of glucocorticoid programming. Whereas a long standing reduction in 11β-HSD-2 activity among survivors is readily interpreted in the context of Holocaust related deprivation, understanding the directional effect on offspring will require replication and further exploration.
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1. Introduction

Disruptions in glucocorticoid metabolism and activity represent enduring consequences of extreme trauma that appear to be at least partially related to age of exposure (Seckl and Holmes, 2007; Yehuda et al., 2010; Yehuda and Seckl, 2011). The persistence of these effects was demonstrated in elderly Holocaust survivors who showed relative deficiencies in the activities of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD-2) and 5α-reductase (Yehuda et al., 2009). In contrast to previously reported endocrine findings in Holocaust survivors, such as reduced basal cortisol levels and increased sensitivity to glucocorticoids (Yehuda et al., 2005b, 2002), the enzymatic alterations observed were not related to the presence or absence of PTSD of other psychiatric disorder in the survivors. Rather, the observed changes were associated with Holocaust exposure. Furthermore, they were particularly prominent in survivors who were youngest at age of exposure to the Holocaust, suggesting a critical developmental window during which adversity could permanently down-regulate glucocorticoid metabolism (Yehuda et al., 2009).

The impacts of Holocaust exposure and related psychopathology have also been examined in the adult offspring of Holocaust survivors. Adult offspring of Holocaust survivors with PTSD, born a median of 15 years after the end of WWII, demonstrated similar reductions in glucocorticoid levels and enhanced glucocorticoid receptor sensitivity (Lehrner et al., 2014; Yehuda et al., 2007a) as had been observed in Holocaust and other trauma survivors with PTSD (Yehuda et al., 2000, 2002). Among adult offspring of Holocaust survivors, lower ambient cortisol was observed specifically in association with maternal PTSD (Yehuda et al., 2007b), an association that has also been demonstrated in offspring of survivors of other traumatic experiences. For example, infants born to mothers who developed PTSD following exposure to the 9/11 attacks in the second and third trimesters of pregnancy also showed lower cortisol compared to infants of similarly exposed mothers who did not develop PTSD (Yehuda et al., 2005a). The trimester effect may reflect differences in maternal 11β-HSD-2 or other placental hormones, peptides, or enzymes that were altered in association with maternal stress. Interestingly, the effects on infants can also be observed if the maternal trauma exposure occurred early in life. Higher cortisol reactivity has been shown for infants of mothers with PTSD as a consequence of childhood abuse (Brand et al., 2010).

In the adult, 11β-HSD-2 is largely confined to the kidney where it contributes to blood pressure regulation. In pregnant women, however, 11β-HSD-2 is highly expressed in the placenta, where it regulates fetal glucocorticoid levels by catalyzing conversion of cortisol to inert cortisone, thus reducing access of high concentrations of maternal cortisol to the umbilical vein (Bertram et al., 2001; Chapman et al., 2013; Drake et al., 2012; Reynolds, 2013). Placental 11β-HSD-2 thus functions to protect the fetus from potentially deleterious effects of maternal stress during pregnancy (Edwards et al., 1993), although this 'barrier' is incomplete since 10—20% of maternal cortisol crosses intact to the fetus (Seckl, 2008). Thus, a relative deficiency in placental 11β-HSD-2, whether as a consequence of exogenous glucocorticoid treatment, maternal stress or nutritional deprivation during pregnancy, or direct inhibition of 11β-HSD-2, results in fetal overexposure to maternal glucocorticoids. Glucocorticoids of fetal and maternal origin play a key role in inducing terminal maturation pathways in fetal organs to prepare for extrauterine life. However, excessive glucocorticoid exposure during gestation may result in the programming of offspring vulnerability to subsequent disease states that become apparent with age. Among these are behavioral disturbances, psychiatric disorders, and conditions related to metabolic syndrome and to cardiometabolic risk, including hypertension (Drake et al., 2007; O'Donnell et al., 2009; Räikkönen et al., 2010; Seckl, 2008; Tang et al., 2011).

The purpose of the current study was to examine 11β-HSD-2 in the adult offspring of Holocaust survivors. Since prior work in Holocaust survivors demonstrated reduced activity of 11β-HSD-2 in association with younger age at exposure, we examined the influence of age of maternal exposure on offspring 11β-HSD-2. We also examined the effect of maternal PTSD on offspring 11β-HSD-2 based on the finding that PTSD severity was a significant correlate of 11β-HSD-2 among Holocaust survivors (Yehuda et al., 2009), and on the significant association of maternal PTSD with glucocorticoid-related alterations in Holocaust offspring (Lehrner et al., 2014; Yehuda et al., 2007a, 2007b). We hypothesized that greatest alterations in 11β-HSD-2 would be present in Holocaust offspring with younger mothers and with mothers with PTSD.

2. Methods

2.1. Subjects

112 Holocaust survivor offspring and comparison subjects were recruited through advertisements requesting Jewish