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CRHR1 genotype and history of maltreatment predict cortisol reactivity to stress in adolescents

Jennifer A. Sumner [a,*], Katie A. McLaughlin [b], Kate Walsh [a], Margaret A. Sheridan [c], Karestan C. Koenen [a]

[a] *Department of Epidemiology, Mailman School of Public Health, Columbia University, 722 W. 168th Street, New York, NY 10032, USA*
[b] *Department of Psychology, University of Washington, 3939 University Way NE, Seattle, WA 98105, USA*
[c] *Developmental Medicine Center, Boston Children's Hospital, Harvard Medical School, 1 Autumn Street, Office 528, Boston, MA 02139, USA*

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Summary This study examined the contributions of a polymorphism of the corticotropin-releasing hormone receptor type I (*CRHR1*) gene (rs110402) and a history of child maltreatment—alone and in interaction—to patterns of cortisol reactivity in adolescents. Adolescents between the age of 13 and 17 years with (n = 61) and without (n = 97) a history of child maltreatment were exposed to the Trier Social Stress Test (TSST). Salivary cortisol was assessed at baseline, and 15 and 30 min after the start of the speech portion of the TSST. Saliva samples for genotyping rs110402 also were collected. Adolescents with one or more G alleles of rs110402, relative to A allele homozygotes, and those exposed to maltreatment, relative to non-exposed adolescents, exhibited blunted cortisol reactivity to the TSST (although these associations approached, but did not reach, the level of statistical significance when accounting for underlying population structure in our racially and ethnically diverse sample). There was also a trend for a stronger child maltreatment association with cortisol hypo-reactivity among G allele carriers, but this association was not statistically significant. Findings suggest that *CRHR1* variation may moderate the downstream effects of child maltreatment on HPA axis function, and implications for understanding mechanisms of risk associated with early adversity are discussed.

* Corresponding author. Tel.: +1 212 342 0401; fax: +1 212 342 5168.
E-mail addresses: js4456@columbia.edu, jennifer.sumner@gmail.com (J.A. Sumner).

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1. Introduction

Child maltreatment is associated with risk for numerous negative outcomes, including mental disorders and adverse physical health outcomes (e.g., Ehlert, 2013). However, considerable variability exists in whether individuals develop health problems following child maltreatment exposure (Ehlert, 2013). Identifying risk and protective factors for negative health sequelae among those exposed to child maltreatment could improve identification of those at greatest risk for experiencing harmful consequences and facilitate better targeting of preventive interventions.

Child maltreatment is associated with numerous neurobiological changes, including hypothalamic-pituitary-adrenal (HPA) axis dysregulation (e.g., Yehuda et al., 2010). The HPA axis regulates neurobiological responses to stress, particularly social and evaluative threats (Dickerson and Kemeny, 2004). Release of corticotropin-releasing hormone (CRH) from the hypothalamus initiates the HPA axis response to stress, which in turn triggers a coordinated neuroendocrine response culminating in cortisol production (Sapolsky et al., 2000). Child maltreatment has been associated with blunted cortisol reactivity to psychosocial stressors (e.g., Carpenter et al., 2007; Fisher et al., 2011; MacMillan et al., 2009). Although the mechanisms underlying this hypo-responsivity are unknown, they might reflect down-regulation of CRH receptors in the pituitary due to hypothalamic CRH hypersecretion following severe or chronic trauma (Fries et al., 2005; Heim et al., 2001), or elevated cortisol production following trauma resulting in heightened negative feedback sensitivity to glucocorticoids, which inhibits hypothalamic CRH production and terminates the HPA axis response after stress (Sapolsky et al., 2000; Stein et al., 1997). There is evidence for heritability of these neuroendocrine disturbances (Yehuda et al., 2010), and regulators of CRH functioning—including genetic influences—may shape the sensitivity of the HPA axis to child maltreatment.

The CRH type 1 receptor (*CRHR1*) gene codes for one of two G-protein coupled CRH receptors (Bittencourt and Sawchenko, 2000). The protein encoded by *CRHR1* is involved in CRH signal transduction, and variants of the gene bind with differential affinity to CRH (Sakai et al., 1998). Variation in *CRHR1* may be associated with risk for psychopathology and other adverse outcomes following child maltreatment. Bradley and colleagues (2008) identified two *CRHR1* single nucleotide polymorphisms (SNPs; rs110402 and rs7209436) that interacted with child maltreatment to predict depressive symptoms in adulthood. For each SNP, maltreatment was associated with higher depressive symptoms among those with the common allele (G for rs110402 and C for rs7209436), whereas the rare allele (A for rs110402 and T for rs7209436) was protective in that maltreated homozygotes did not exhibit elevated depressive symptoms compared to non-maltreated homozygotes. Similar results emerged based on the common TAT haplotype (formed by rs7209436, rs110402, and rs242924). The interaction of *CRHR1* genotype with child maltreatment in predicting depression has been replicated in several studies (Heim et al., 2009; Polanczyk et al., 2009). *CRHR1* variants also have been associated with posttraumatic stress symptoms following pediatric injury trauma (Amstadter et al., 2011).

Given the critical role of CRH in HPA axis regulation, *CRHR1* genotype might moderate the effects of child maltreatment on HPA axis reactivity. In young rhesus macaques, *CRHR1* polymorphisms were related to increased metabolic activity in the amygdala and hippocampus in response to stress (Rogers et al., 2013). These associations were observed in ''healthy'' macaques reared in typical environments, suggesting that particular *CRHR1* genotypes may be associated with maladaptive stress responses even in the absence of environmental adversity or psychopathology. In humans, differences in brain activity during an emotional word processing task as a function of rs110402 genotype have been observed (Hsu et al., 2012).

Several studies have examined associations between *CRHR1* variants and cortisol regulation, although sample characteristics, specific SNPs, and cortisol metrics vary across investigations. For example, healthy adults homozygous for the minor alleles of rs7209436, rs110402, and rs242924 had lower peak cortisol responses to a psychosocial stress task compared to major allele carriers (Mahon et al., 2013). However, this study did not consider child maltreatment history. In investigations of adults reporting child maltreatment, cortisol response to the dexamethasone/CRH test was higher among homozygotes for the major allele of rs110402 compared to minor allele carriers (Heim et al., 2009; Tyrka et al., 2009), although this effect was only observed in men in one study (Heim et al., 2009). In a community sample of preschool-aged children, carriers of the minor (A) allele of rs17763104 exhibited greater cortisol reactivity to a stress task compared to major (G) allele homozygotes (Sheikh et al., 2013). *CRHR1* has also been associated with diurnal cortisol rhythms. Youths with two copies of the TAT haplotype and a history of maltreatment exhibited a flatter diurnal cortisol slope than those without maltreatment exposure; no differences as a function of maltreatment history were observed for those with zero or one copies of the haplotype (Cicchetti et al., 2011).

Taken together, existing evidence suggests that *CRHR1* variants influence cortisol responses to stress. However, the extent to which *CRHR1* polymorphisms moderate the effect of child maltreatment on cortisol reactivity to psychosocial stress is not clear. Furthermore, no studies have examined whether *CRHR1* genotype and child maltreatment contribute jointly to cortisol reactivity in adolescents. The HPA axis undergoes significant changes from childhood to adolescence, such that adolescents show increased physiological stress responses compared to children (Stroud et al., 2009). Adolescence is also associated with increased incidence of numerous psychiatric disorders (Kessler et al., 2005), and changes in stress reactivity during adolescence may contribute to vulnerability to psychopathology in at-risk youth (e.g., Spear, 2009). Examining genetic influences on stress reactivity during adolescence may aid in identifying those most susceptible to dysregulation during this developmental stage.

The current study examined associations of a SNP in *CRHR1* (rs110402) with cortisol reactivity to a psychosocial stressor in adolescents alone and in interaction with child maltreatment. Based on previous research (e.g., MacMillan et al., 2009; Sheikh et al., 2013), we anticipated significant main effects of genotype and maltreatment history on cortisol reactivity. Furthermore, given that child maltreatment has