Interaction of Childhood Maltreatment with the Corticotropin-Releasing Hormone Receptor Gene: Effects on Hypothalamic-Pituitary-Adrenal Axis Reactivity

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Background: Variation in the corticotropin-releasing hormone receptor (*CRHR1*) gene has been shown to interact with early life stress to predict adult depression. This study was conducted to determine whether *CRHR1* polymorphisms interact with childhood maltreatment to predict hypothalamic-pituitary-adrenal (HPA) axis reactivity, which has been linked to both depression and early life stress.

Methods: One hundred twenty-nine White, non-Hispanic adults completed the Childhood Trauma Questionnaire and the dexamethasone/corticotropin-releasing hormone (DEX/CRH) test, and provided blood samples for genotyping of two *CRHR1* polymorphisms.

Results: Both rs110402 and rs242924 (which were in tight linkage disequilibrium, $D' = .98$) showed a significant interaction with maltreatment in the prediction of cortisol response to the DEX/CRH test ($p < .05$). For subjects with maltreatment, the GG genotype of each single nucleotide polymorphism was associated with elevated cortisol responses to the test.

Conclusions: Variation in the CRHR1 moderates the effect of childhood maltreatment on cortisol responses to the DEX/CRH test. Excessive HPA axis activation could represent a mechanism of interactions of risk genes with stress in the development of mood and anxiety disorders.

Key Words: Cortisol, CRH test, *CRHR1* gene, DEX, gene–environment interaction, genetics, HPA axis

Stressful life experiences increase risk for psychiatric disorders such as major depression and anxiety disorders. Genes that moderate the influence of adversity on depressive and anxiety disorders have recently been identified (1–3). One likely mechanism of gene–environment interactions is that risk genes might confer sensitivity to stress, possibly through altered functioning of corticotropin-releasing hormone (CRH) and the hypothalamic-pituitary-adrenal (HPA) axis. Studies of rodents and nonhuman primates with early exposure to stress show enduring alterations of behavior as well as activity of CRH and the HPA axis, changes that parallel some of the abnormalities frequently seen in major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) (4). Recent studies of humans have also found associations between childhood adversity and enhanced or attenuated CRH and HPA axis function (5–8). Preclinical work demonstrates that prolonged or excessive exposure to stress and glucocorticoids results in neurostructural changes in limbic brain regions that might contribute to the pathogenesis of stress-related disorders (9,10).

Genes that regulate activity of CRH and the HPA axis are likely determinants of the effects of stress and adversity on risk for depressive and anxiety disorders. Recent studies have examined variation in the gene coding for the CRH type I receptor, which mediates the hormonal and behavioral effects of CRH in response to stress (11). Corticotropin-releasing hormone receptors have been found to occupy widespread areas of the primate brain, including the pituitary, amygdala, hippocampal formation, and throughout the neocortex; the CRH type 1 receptor is also expressed in cerebellar cortex, locus coeruleus, thalamus, nucleus of the solitary tract and striatum (12–14).

Variation in the *CRHR1* gene has been linked to major depression (2,15,16). Bradley *et al.* (2) recently found that several single nucleotide polymorphisms (SNPs) in this gene interacted with childhood maltreatment to predict depressive symptoms and in two separate samples found that a haplotype of the three most significant SNPs was protective against depressive symptoms among maltreated subjects as measured by the Childhood Trauma Questionnaire (CTQ). Polanczyk *et al.* (16) recently replicated the interaction of this haplotype and maltreatment according to the CTQ on the prediction of major depressive disorder in a representative community sample but not in another community cohort with a different measure of maltreatment. A gene × stress interaction influencing excessive alcohol use among adolescents has also been demonstrated (17).

Recent reports have identified HPA axis effects of genes linked to depression and anxiety (e.g., 18–20). A preliminary study showed altered neuroendocrine function in relation to variation in the *CRHR1* gene in a sample of adolescents (20). These studies have not examined influences of early adversity. In the current study, we tested the hypothesis that two of the *CRHR1* polymorphisms studied by Bradley *et al.* (2) and Polanczyk *et al.* (16) would interact with reported childhood maltreatment to predict altered cortisol responses to the dexamethasone (DEX)/CRH test.

Methods and Materials

Subjects

Participants were 78 women and 51 men. Subjects were recruited from the community via flyers as well as through

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Internet and newspaper advertisements for "healthy adults" and "healthy adults with a history of early-life stress." Only individuals who reported their race as White, non-Hispanic (not Black, Asian, Pacific Islander, Native American, or "Other") were included in the present study, to reduce the possibility of population stratification. Individuals with lifetime psychotic disorders and bipolar disorder were excluded from participation, and the current study also excluded those with current alcohol or substance abuse or dependence, current MDD, and current PTSD, due to possible neuroendocrine effects of these disorders. Participants completed a medical history, physical examination, electrocardiogram, and standard laboratory studies to rule out acute or unstable medical illness, endocrine disease, or ongoing treatment with drugs that might influence HPA axis function, including psychotropics, β blockers, angiotensin-converting enzyme inhibitors, ketoconazole, metyrapone, and corticosteroids. Oral contraceptives were permitted. Subjects gave voluntary written informed consent to participate in this study, which was approved by the Butler Hospital Institutional Review Board.

Measures

The Structured Clinical Interview for DSM-IV. Current and lifetime history of Axis I psychiatric diagnoses were assessed with the Structured Clinical Interview for DSM-IV (SCID) (21).

CTQ. The 28-item version of the CTQ (22) was used to assess childhood maltreatment. The five CTQ subscales (physical abuse, sexual abuse, emotional abuse, physical neglect, emotional neglect) were significantly intercorrelated in this sample with r values ranging from .68 to .70 for most pairs of subscales. Correlations of sexual abuse and physical abuse with the other subscales were weaker, and r values ranged from .31 to .67. Childhood maltreatment was defined as a "moderate to severe" score on any of five subscales. The remaining participants were considered to have no/minimal maltreatment according the CTQ.

Genotyping

DNA was extracted from frozen whole blood with standard methods. Two of the individual *CRHR1* SNPs that have previously been reported to interact with reported childhood maltreatment in the prediction of depression (2), rs110402 located in intron one and rs242924 from intron 2 (which are approximately 5 kb apart), were genotyped in the present study. Markers were genotyped with a fluorogenic 5′ nuclease assay (the TaqMan method) (23). All samples were genotyped in duplicate for quality control. Genotyping failed or provided ambiguous genotype results from seven subjects for the rs110402 SNP and three subjects for rs242924; these participants were therefore missing from the relevant analyses.

Table 1. Characteristics of Participants According to Childhood Maltreatment

	No/Minimal Maltreatment $n = 91$	Moderate/Severe Maltreatment $n = 38$	p
Age, Mean (SD)	26.7 (8.78)	35.9 (11.65)	<.001
Range	18–61	19–58	
Gender, *n* (%)			
Male	40 (44.0)	11 (28.9)	
Female	51 (56.0)	27 (71.1)	ns
BMI, Mean (SD)	25.1 (3.3)	27.0 (5.1)	<.05
Range	20.1–34.8	19.4–40.8	
Genotype, *n* (%)			
SNP rs242924 ($n = 126$)			
GG	27 (30.3)	11 (29.7)	
GT	46 (51.7)	19 (51.4)	
TT	16 (18.0)	7 (18.9)	ns
SNP rs110402 ($n = 119$)			
GG	22 (26.8)	10 (27.0)	
AG	44 (53.7)	20 (54.1)	
AA	16 (19.5)	7 (18.9)	ns
Type of Maltreatment, *n* (%)[a]			
Emotional abuse	0	19 (50.0)	—
Physical abuse	0	8 (21.1)	—
Sexual abuse	0	17 (44.7)	—
Emotional neglect	0	21 (55.3)	—
Physical neglect	0	14 (36.8)	—
SCID "Probable" Lifetime Axis I Diagnoses, *n* (%)			
Major depressive episode	14 (15.4)	12 (31.6)	<.05
Dysthymic disorder	2 (2.2)	3 (7.9)	ns
Alcohol abuse/dependence	7 (7.7)	8 (21.1)	<.05
Drug abuse/dependence	6 (6.6)	3 (7.9)	ns
PTSD	1 (1.1)	2 (5.3)	ns
Panic disorder or social phobia	1 (1.1)	2 (5.3)	ns

BMI, body mass index; SNP, single nucleotide polymorphism; SCID, Structured Clinical Interview for DSM-IV; PTSD, posttraumatic stress disorder.

[a]Percentages for types of maltreatment do not add up to 100%, because participants could report more than one type of maltreatment. Subjects were excluded if they met the criteria for lifetime psychotic disorder, bipolar disorder, current alcohol or drug abuse or dependence, major depression, or post-traumatic stress disorder. No participant had a lifetime diagnosis of generalized anxiety disorder.