Functional Effects of Polymorphisms in the Human Corticotropin-Releasing Hormone Receptor 1 (CRHR1) Gene

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ABSTRACT

The role of the hypothalamic-pituitary-adrenal (HPA) axis in stress-related psychiatric disorders (i.e., depression and anxiety) has been well-established. Recent data indicate that corticotropin-releasing hormone (CRH), the principal neuroregulator of the HPA axis, plays a key role in alcohol dependence and that a gene-environment interaction between a SNP (rs1876831) in the CRH receptor 1 (CRHR1) gene and stressful life events predicts binge-drinking in adolescents. Our group previously identified a CRHR1 promoter SNP (rs12938031) that predicted a more robust HPA axis response to CRH stimulation in AA homozygotes (Thode et al, unpublished).

This study examines the impact of CRHR1 expression at the level of the amygdala following a history of alcohol dependence.

MATERIALS AND METHODS

• Subjects from the ongoing Teen Alcohol Outcomes Study (TAOS), an ongoing cohort study of the long-term outcome of early risk factors. Subjects included adolescents aged 12 to 15 years.

DNA was obtained from saliva (n=340), and a subset had an fMRI (n=57). Lymphoblastoid cell lines of 12 homozygotes for rs12938031 were selected (6 AA and 6 GG) to determine CRHR1 mRNA levels. Linkage disequilibrium (LD) analyses were carried out using Haploviz 4.1. Imaging analyses were done using GLM in SPM5, and for baseline mRNA levels, unpaired t-tests were used. SNPs rs12938031 and rs1876831 were found to be in high LD (D' = 0.951, LOD = 35.6, p<0.001). rs12938031 GG homozygotes were associated with less bilateral amygdala reactivity (left: p<0.001, right: p=0.05) and greater left ventral striatum reactivity (p=0.039) and trended toward lower expression of CRHR1 (p=0.055) as compared to AA homozygotes. These results provide additional evidence for genetic moderation of the stress response directly involving a SNP (rs12938031) in the promoter of CRHR1. Our ongoing work is examining whether this moderation stems from baseline and/or stress-induced differences in CRHR1 expression.

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REFERENCES

