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Cortisol and behavior in fragile X syndrome

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Abstract

Objective: The purpose of this study was to determine if children with fragile X syndrome, who typically demonstrate a neurobehavioral phenotype that includes social anxiety, withdrawal, and hyper-arousal, have increased levels of cortisol, a hormone associated with stress. The relevance of adrenocortical activity to the fragile X phenotype also was examined.

Method: One hundred and nine children with the fragile X full mutation (70 males and 39 females) and their unaffected siblings (51 males and 58 females) completed an in-home evaluation including a cognitive assessment and a structured social challenge task. Multiple samples of salivary cortisol were collected throughout the evaluation day and on two typical non-school days. Measures of the fragile X mental retardation (*FMR1*) gene, child intelligence, the quality of the home environment, parental psychopathology, and the effectiveness of educational and therapeutic services also were collected. Linear mixed-effects analyses were used to examine differences in cortisol associated with the fragile X diagnosis and gender (fixed effects) and to estimate individual subject and familial variation (random effects) in cortisol hormone levels. Hierarchical multiple regression analyses were conducted to determine whether adrenocortical activity is associated with behavior problems after controlling for significant genetic and environmental factors.

Results: Results showed that children with fragile X, especially males, had higher levels of salivary cortisol on typical days and during the evaluation. Highly significant family effects on salivary cortisol were detected, consistent with previous work documenting genetic and environmental influences on adrenocortical activity. Increased cortisol was significantly asso-

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ciated with behavior problems in boys and girls with fragile X but not in their unaffected siblings.

Conclusions: These results provide evidence that the function of the hypothalamic-pituitary-adrenal axis may have an independent association with behavioral problems in children with fragile X syndrome.

Keywords: Fragile X syndrome; Cortisol; Stress; Neuroendocrine; Behavior; FMRP

1. Introduction

Fragile X syndrome, caused by mutations in a single gene on the long arm of the X chromosome, occurs in 1 of every 2000 to 5000 live births and is the most common known inherited cause of developmental disability. The cytogenetic fragile site on the X chromosome from which the syndrome derives its name is typically caused by the presence of more than 200 cytosine-guanine-guanine (CGG) triplet repeats within the promoter region of the fragile X mental retardation (*FMR1*) gene, which prevents normal transcription. This "transcriptional silencing" of the gene and the subsequent diminished or absent production of the *FMR1* protein (FMRP) results in aberrant brain development and function (Devys et al., 1993; Tamanini et al., 1997). Because females have two X chromosomes, production of FMRP is maintained to varying degrees by the presence of the unaffected X chromosome. Consequently, females tend to be less severely affected by fragile X than males.

In addition to cognitive impairment, individuals with fragile X typically demonstrate a neurobehavioral phenotype that includes stress-related symptoms such as hyper-arousal, hyper-responsivity to sensory stimuli, hyperactivity, impulsivity, gaze aversion, and social anxiety and withdrawal (Cohen et al., 1988; Lachiewicz, 1992; Freund et al., 1993; Lachiewicz and Dawson, 1994; Cohen, 1995; Mazzocco et al., 1998). Recently, FMRP expression has been linked to some of these phenotypic characteristics of fragile X, including social withdrawal, anxiety and depression (Hessl et al., 2001). Despite the relatively consistent links between *FMR1* gene function and outcomes in fragile X, considerable variability in stress-related behavior problems exists, ranging from high levels of distress, often in novel social situations, to normal functioning. This variability can in part be explained by non-genetic factors, such as characteristics of the home environment and the effectiveness of educational and therapeutic services (Hessl et al., 2001). However, other individual characteristics of children or the environments in which they live may help to better account for these individual differences, leading to more effective methods of assessment and treatment of stress-related symptoms.

One such individual characteristic, the function of the hypothalamic-pituitary-adrenal (HPA) axis, may help to explain some of the variability in stress-related symptoms among children with fragile X. Regulation of the HPA axis is complex and involves feedback mechanisms occurring at the level of the hypothalamus, pituitary, hippocampus, and frontal cortex. This dynamic system is mediated through the secretion of adrenal glucocorticoid hormones, and is involved in the regulation of