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Cortisol circadian rhythms and response to stress in children with autism☆

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Summary *Background*: Autism is a severe neurodevelopmental disorder characterized by impairment in communication, social interaction, repetitive behaviors and difficulty adapting to novel experiences. The Hypothalamic-Pituitary-Adrenocortical (HPA) system responds consistently to perceived novel or unfamiliar situations and can serve as an important biomarker of the response to a variety of different stimuli. Previous research has suggested that children with autism may exhibit dysfunction of the HPA system, but it is not clear whether altered neuroendrocrine regulation or altered responsiveness underlies the differences between children with and without autism. In order to provide preliminary data concerning HPA regulation and responsiveness, we compared circadian rhythms and response to a non-social, environmental stressor in children with and without autism.

Methods: Circadian rhythms of cortisol were estimated in children with ($N=12$) and without ($N=10$) autism via analysis of salivary samples collected in the morning, afternoon and evening on 2 consecutive days. HPA responsiveness was assessed by examining the time course of changes in salivary cortisol in response to a mock MRI.

Results: Both groups showed expected circadian variation with higher cortisol concentration in morning than in the evening samples. The children with autism, but not typical children, showed a more variable circadian rhythm as well as statistically significant elevations in cortisol following exposure to a novel, nonsocial stimulus.

Conclusions: The results suggest that children with autism process and respond idiosyncratically to novel and threatening events resulting in an exaggerated cortisol response.

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1. Introduction

Autism is a severe neurodevelopmental disorder characterized by qualitative impairment before the age of three in verbal and nonverbal communication, reciprocal social interaction, and a markedly restricted repertoire of activities and interests (APA, 1994). In addition to these features, children with autism have been described as experiencing difficulty tolerating novelty and environmental stressors (Kanner, 1943). Amongst the two most frequently used indices of the response to stress have been observable changes in the behavior of an individual experiencing stress and the marked increase in the stress related hormones. When the behavior and the endocrine markers of stress are concordant there is little problem in interpreting the outcome. However, there are examples of dissociation between these behavioral and endocrine measures (e.g. Wiener et al., 1988). In children with autism, there are excessive behavioral reactions to stressful circumstances, but it is less clear whether or not this is accompanied by a corresponding increase in neuroendocrine activity.

The hypothalamic-pituitary-adrenal (HPA) axis is the classical endocrine stress system. Although the label HPA is still used to describe this system, it is abundantly clear that the regulation of the HPA axis involves a complex neural system involving many different anatomical structures and neurochemical events that are required to activate and/or inhibit the HPA axis. Adrenocorticotropic hormone (ACTH) is regulated by two primary molecules at opposing ends of the system, which are corticotropin releasing hormone (CRH) in the brain, which activates both behavioral and hormonal stress responses and glucocorticoids (cortisol in humans) secreted from the adrenal which acts primarily to inhibit the release of CRH, ACTH and cortisol through its action on the glucocorticoids receptors in the brain and the pituitary. Thus, one of the most widely used biological markers of stress is the release of cortisol from the adrenal since elevations often occur in response to novel and unpredictable situations (Gunnar and Donzella, 2002; Hennessey and Levine, 1979).

It has been established that the regulation of the HPA axis is different depending on the type of stress the organism is exposed to. The most recent descriptions of these differences have been elaborated by Herman and Cullinan (1997). Thus, although seemingly disparate stimuli activate the HPA axis they utilize different pathways. Systemic stressors are physical and context-independent and are capable of activating the HPA system in unconscious animals. In general, systemic stimuli usually involve a life-threatening event. In the case of systemic stimuli, the information required to activate the HPA system is relayed to the periventricular nuclei (PVN) of the hypothalamus via the brain stem. In contrast, processive stimuli are context dependent, requiring the comparison of current information with past experience and the assignment of emotional meaning. Limbic system structures are the primary mediators of processive stimuli. Thus the bed nucleus of the stria terminalis (BNST) preoptic nucleus, lateral and medial septum, the amygdala, prefrontal cortex and hippocampus all are involved in either activation or inhibition of the stress response to processive stimuli. Given the importance of the limbic system in the regulation of the stress response it has become more common to refer to the stress responsive system as the LHPA axis. The 'L' refers to the limbic system.

There is evidence that regulation of the HPA system may be dysfunctional in children with autism (Nir et al., 1995; Richdale and Prior, 1992; Yamazaki et al., 1975). Most of the published reports examining HPA responsiveness in children with autism have serious methodological flaws, which include a lack of appropriate controls, invasive sampling techniques, mixed diagnosis and very small samples. Children with autism have been shown to exhibit an exaggerated stress response as evidenced by increases in ACTH and beta-endorphin following an injection of insulin (Maher et al., 1975). In this investigation, there were no controls for the effects of venipuncture per se. Tordjman et al. (1997) and Curin et al. (2003) report higher levels of ACTH in autism. These data were interpreted as indicating that individuals with autism have a chronic level of anxiety. However, in these studies cortisol was not different or lower than controls. Insofar as the release of ACTH is much more rapid than cortisol, it appears more likely that the higher ACTH levels observed in the subjects with autism was a result of the response to venipuncture and restraint required to obtain blood samples. Richdale and Prior (1992) provide additional support for the hypothesis that children with autism may be hyperresponsive to environmental stress. Subjects with autism who were integrated into the regular school system showed hypersecretion of cortisol suggesting an environmental stress response in the school environment. In contrast, a recent report showed a lack of salivary cortisol elevation or 'hyporesponsiveness' in a group of autistic-like children diagnosed with Multiple Complex Developmental Disorder (MCDD; Jansen et al., 2000). These investigators exposed