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A review of rhythm and responsiveness of cortisol in individuals with autism spectrum disorders

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Abstract Examination of the hypothalamic—pituitary—adrenal (HPA) axis via cortisol among individuals with autism spectrum disorder (ASD) has been a growing area of research interest. The following review includes investigations of cortisol conducted with cohorts of individuals with ASD across the lifespan over the past four decades. In general, studies find dysregulation when examining the diurnal rhythm as a whole in lower functioning children with ASD; however, limited evidence exists for alterations in higher functioning individuals and in specific aspects of the diurnal cycle (cortisol awakening response, daily decline, variability) relative to typically developing individuals. Studies examining the responsiveness of cortisol in ASD suggest an overall sluggishness of the HPA axis in responding to physiological or physical manipulation. Hypo-responsiveness was observed in stressors that involve social evaluative threat, however, hyper-responsiveness of the HPA axis was observed in situations involving unpleasant stimuli or relatively benign social situations. A number of important considerations when conducting studies of cortisol in ASD cohorts are discussed.

Cortisol, the primary glucocorticoid in humans, is released from the adrenal cortices of the hypothalamic—pituitary—adrenal (HPA) axis. It produces a variety of effects throughout the body including influences on cardiovascular function, immunity, metabolism, and neurobiology (Sapolsky et al., 2000), which collectively allow optimal adaptation to changing environmental demands. However, prolonged activation can have deleterious effects as seen in chronic stress resulting in suppression of the immune system (e.g., Munck and Guyre, 1991; Derijk and Sternberg, 1994). In addition to being involved in several vital biological processes and interactions, cortisol is central to the physiological response

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to physical or perceived psychological stress (Hennessey and Levine, 1979; Herman and Cullinan, 1997).

The diurnal rhythm and responsiveness of cortisol has been evaluated in autism spectrum disorder (ASD), a neurodevelopmental disorder characterized by impairment in social communication, restricted interests, and repetitive behaviors (American Psychiatric Association, 2013). Presumably as a result of these challenges, individuals with ASD often experience poor adaptation to change. Therefore, examination of the HPA axis via cortisol has been a growing area of research interest. The following review includes investigations of cortisol conducted with cohorts of individuals with ASD across the lifespan over the past four decades. While we collectively refer to the population as ASD, the review will use the appropriate nomenclature of the studies (e.g., autistic disorder, Asperger syndrome) whenever possible. Historically, children who currently meet criteria for ASD would have been diagnosed with autistic disorder (significant impairment in social functioning, communication, and restricted, repetitive behavior), pervasive developmental disorder—not otherwise specified (deficits in all three domains to a lesser degree) or Asperger syndrome (deficits in social functioning and restricted behavior but an absence of delays in language) (American Psychiatric Association, 2000).

Circulating cortisol can be measured in blood, saliva or urine, and they are correlated with each other (Goodyer et al., 1996), with high agreement between blood and saliva (Kirschbaum and Hellhammer, 2000). However, there are distinctions in the extent to which it may be bound versus free, as well as the timing to detect differences in response to stressors. Free or unbound cortisol is the portion that is not bound to circulating proteins, such as corticosteroid binding globulin (CBG), and according to the Free Hormone Hypothesis, it is the biologically active fraction of cortisol that is relevant (Mendel, 1989; see Levine et al., 2007, for a critical review). Cortisol in serum is 80% bound to CBG and 10% to serum albumin (Heyns et al., 1967). Serum cortisol requires phlebotomy, which may be stressful; therefore, less invasive methods, such as salivary collection are often employed especially in children. Salivary cortisol levels reflect 70% of the serum free cortisol levels (Vining et al., 1983). Urinary cortisol is non-invasive, collected over a 24 h period. It serves as a direct assessment of free circulating cortisol and is not impacted by factors that affect CBG levels (Newell-Price et al., 2006). However, cortisol in urine is a relatively minor proportion as it consists primarily of metabolite breakdown products. The detection of cortisol in the periphery lags by 5—20 min with the transfer of cortisol from plasma to saliva occurring within less than a minute (Kirschbaum and Hellhammer, 2000). Changes in urinary free cortisol levels occur with a lag of approximately 4 h (Morineau et al., 1997). All of these methods have been employed in the study of individuals with ASD.

1. Rhythm of cortisol in ASD

1.1. Overall rhythm

Table 1 summarizes studies that have examined the rhythm of cortisol in ASD samples. The earliest studies of basal cortisol in ASD focused on examination of the overall diurnal (daily waking hours) or circadian (24-hour cycle) rhythm. The normal circadian pattern of cortisol is a sharp increase in the morning hours, with a gradual decline throughout the day until it reaches its nadir during nighttime sleep (Smyth et al., 1997); deviation from this pattern is suggestive of HPA-axis dysregulation. In contrast to other studies (described later) that have focused on specific aspects of this pattern (e.g., cortisol awakening response, daily decline, variability), these studies examined global regulation or dysregulation.

Using plasma cortisol collected at 6-hour intervals from children with autistic disorder, Yamazaki et al. (1975) found that only two of seven children in their sample had the expected diurnal pattern. In another earlier study, Hill et al. (1977) reported greater abnormality in circadian patterns of cortisol, assayed from plasma collected over 24 h, for children with autistic disorder relative to typically developing (TD) children. Similarly, Hoshino et al. (1987) reported that compared to TD adults (all of whom showed a normal diurnal rhythm) and children (of whom 96% showed a normal diurnal rhythm), children with ASD were more likely to have abnormalities in the circadian pattern of cortisol—particularly those children whom they defined as lower functioning. More recent studies of children and adolescents with autistic disorder (Corbett et al., 2009; Richdale and Prior, 1992) also suggest greater circadian dysregularity in ASD groups relative to age-matched TD controls.

There has only been one study that measured overall level of circulating cortisol for individuals with ASD. Using 24-hour urine, Marinović-Ćurin et al. (2008) found no significant differences in total daily cortisol secretion between their sample of children/adolescents with autistic disorder, and age-matched TD controls. Thus, although patterns of diurnal rhythm appear to be abnormal for individuals with ASD, this study suggests that overall cortisol output in the system is similar to controls.

More recent investigations of basal cortisol in individuals with ASD have focused on specific aspects of the diurnal cycle, namely, the cortisol awakening response (CAR), the daily decline, and variability both within-person and within-group. Findings related to each of these aspects of the diurnal cycle are described below.

1.2. Cortisol awakening response (CAR)

The CAR is a sharp increase of cortisol approximately 30-minutes after waking that is distinct from the normal circadian rhythm and occurs in roughly 77% of individuals (Pruessner et al., 1997; Wust et al., 2000). It is postulated that the CAR is a measure of the reactive capacity of the HPA axis (Schmidt-Reinwald et al., 1999) and may serve a preparatory role in assisting the organism to prepare the body for upcoming challenges during the day (Fries et al., 2009). Developmental factors may influence the presence and magnitude of the CAR, which has resulted in some investigators establishing different child and adult criteria (Gunnar et al., 2009b; Kudielka and Kirschbaum, 2003). In adults, the CAR has been defined as a significant rise in cortisol of 2.49 nmol or greater (Wust et al., 2000). Since children