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Dysregulation of the cortisol diurnal rhythm following prenatal alcohol exposure and early life adversity

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ABSTRACT

The hypothalamic-pituitary-adrenal (HPA) axis is impacted by a multitude of pre- and postnatal factors. Developmental programming of HPA axis function by prenatal alcohol exposure (PAE) has been demonstrated in animal models and in human infants, but remains understudied in older children and adolescents. Moreover, early life adversity (ELA), which occurs at higher rates in children with PAE than in non-exposed children, may also play a role in programming the stress response system. In a cohort of children and adolescents with PAE and ELA (PAE + ELA), we evaluated HPA function through assessment of diurnal cortisol activity compared to that in typically developing controls, as well as the associations among specific ELAs, adverse outcomes, protective factors, and diurnal cortisol. Morning and evening saliva samples were taken under basal conditions from 42 children and adolescents (5–18 years) with PAE + ELA and 43 typically developing controls. High rates of ELA were shown among children with PAE, and significantly higher evening cortisol levels and a flatter diurnal slope were observed in children with PAE + ELA, compared to controls. Medication use in the PAE + ELA group was associated with lower morning cortisol levels, which were comparable to controls. Complex associations were found among diurnal cortisol patterns in the PAE + ELA group and a number of ELAs and later adverse outcomes, whereas protective factors were associated with more typical diurnal rhythms. These results complement findings from research on human infants and animal models showing dysregulated HPA function following PAE, lending weight to the suggestion that PAE and ELA may interact to sensitize the developing HPA axis. The presence of protective factors may buffer altered cortisol regulation, underscoring the importance of early assessment and interventions for children with FASD, and in particular, for the many children with FASD who also have ELA.

Introduction

Children with Fetal Alcohol Spectrum Disorder (FASD) experience a range of effects following prenatal alcohol exposure (PAE) including central nervous system (CNS) alterations involving cognitive and behavioral function, and in approximately 10% of diagnosed cases, physical indicators, including characteristic facial dysmorphology and/or growth restriction (Astley, 2010; Chudley et al., 2005; Stratton, Howe, & Battaglia, 1996). Deficits in self-regulation and adaptive functioning can occur across the FASD spectrum (Mattson, Crocker, & Nguyen, 2011; Riley, Infante, & Warren, 2011), and alterations in the activity and regulation of the hypothalamic-pituitary-adrenal (HPA) or stress axis may be a physiological marker of these deficits (Bauer, Quas, & Boyce, 2002). The HPA axis is a key component of the stress response system and is shaped or programmed by both pre- and postnatal early life experiences (Kapoor, Dunn, Kostaki, Andrews, & Matthews, 2006; Smith & Vale, 2006), including PAE (Haley, Handmaker, & Lowe,

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2006; Jacobson, Bihun, & Chiodo, 1999; Oberlander et al., 2010; Ramsay, Bendersky, & Lewis, 1996).

The typical circadian rise and fall of cortisol is necessary to support normal brain growth and to sustain general functioning. Cortisol is released at higher levels in the morning to mobilize physiological resources and self-regulatory processes. Over the course of the day cortisol levels decrease as the body regulates resources. There is some research on the association between PAE and cortisol secretion in humans; however, studies have been largely limited to the neonatal and toddler periods. Ramsay et al. (1996) found higher pretest cortisol levels and blunted cortisol responses to medical inoculation procedures in 2-month-old infants exposed to alcohol and cigarettes prenatally. Similar results were found in neonates with PAE following a heel-lance blood draw procedure (Oberlander et al., 2010). Jacobson et al. (1999) found that heavy PAE was associated with both higher basal levels and greater cortisol reactivity to a heel-lance blood draw in 13-month-old toddlers, indicating that reactivity may increase with age. Sexually dimorphic effects have also been found in stress reactivity studies. For example, Haley et al. (2006) demonstrated higher cortisol reactivity in 5- to 7-month-old infants with PAE in response to a "still face" paradigm, but only among boys born to mothers who were high-frequency drinkers, compared to those born to low-frequency drinkers. Ouellet-Morin et al. (2011) found disrupted patterns of cortisol activity in 19-month-old boys, but not girls, with low-level PAE, including both lower baseline levels and higher post-stress reactivity. To our knowledge, only one study has examined cortisol activity under baseline conditions in older, school-aged children and adolescents with FASD. Keiver, Bertram, Orr, and Clarren (2015) found that 8- to14-year-old children with FASD had significantly higher afternoon and evening cortisol levels and a trend toward lower morning levels compared to controls, suggesting the possibility of a disturbance in normal basal HPA regulation over the day. Animal studies support and extend these findings, demonstrating HPA hyper-responsiveness following PAE, with increased activation and/or delayed recovery of HPA activity following both acute and repeated stressors, as well as alterations in basal corticosterone levels over the day and changes in central HPA regulation (Hellemans, Sliwowska, Verma, & Weinberg, 2010; Schneider, Moore, & Adkins, 2011; Schneider, Moore, & Kraemer, 2004; Schneider, Moore, Kraemer, Roberts, & DeJesus, 2002; Weinberg, Sliwowska, Lan, & Hellemans, 2008).

Compounding the impact of PAE, children with FASD often experience both early life adversity (ELA) (e.g., maltreatment, early caregiving disruption and contact with the foster care system, poverty, and familial adversity), and later adverse outcomes (e.g., school failure, contact with the criminal justice system, victimization, and comorbid mental health problems) at high rates (Astley, 2010; Coggins, Timler, & Olswang, 2007; Streissguth et al., 2004; Yumoto, Jacobson, & Jacobson, 2008). Both pre- and postnatal experiences are known to play a key role in early programming of the stress response system and are likely important moderators of fetal programming following both PAE and ELA (Bosch et al., 2012; Entringer, Kumsta, Hellhammer, Wadhwa, & Wüst, 2009; Essex, Klein, Cho, & Kalin, 2002; Glover, O'Connor, & O'Donnell, 2010; Lupien, McEwen, Gunnar, & Heim, 2009; Weinstock, 2008). Factors at the parenting level (stress, psychopathology, high psychosocial risk, ongoing substance abuse, abuse during pregnancy, maternal sensitivity, quality of parent–child interactions), child level (maltreatment), and environmental level (poverty/socioeconomic status, familial adversity) are all linked with later cortisol dysregulation (Hunter, Minnis, & Wilson, 2011). Exposure to early and chronic stress can lead to dysregulation of the HPA axis by middle childhood and has been linked with both short- and long-term physical, behavioral, cognitive, and mental health problems (Brand et al., 2010; Cicchetti, Rogosch, Gunnar, & Toth, 2010; Gunnar, Frenn, Wewerka, & Van Ryzin, 2009; Suor, Sturge-Apple, Davies, Cicchetti, & Manning, 2015). Results vary across studies, but generally speaking, acute stressors are associated with hyper-responsiveness of the HPA axis and higher cortisol levels, whereas hypo-responsiveness and lower cortisol levels may be seen as a consequence of chronic stress and overstimulation of the axis (Fries, Hesse, Hellhammer, & Hellhammer, 2005; Gunnar, Fisher, & Early Experience, Stress, and Prevention Network, 2006; Gunnar & Vazquez, 2001). A "dual-vulnerability" theory has also been supported, wherein individuals with multiple vulnerabilities, such as altered stress reactivity and impaired cognitive functioning, may be especially prone to later problems in everyday living (Robinson, Ode, & Hilmert, 2011).

In addition to risk factors linked with poor developmental outcomes, a number of protective factors have been identified as playing important moderating roles in reducing adverse outcomes for children with PAE, including early assessment, diagnosis, intervention, and the quality and stability of the home environment (McLachlan et al., in preparation; Rasmussen, 2012; Streissguth et al., 2004). Critically, evidence from young children (without PAE) suggests that altered cortisol activity and regulation can be ameliorated following improvements in care and interventions targeting self-regulatory deficits (Hunter et al., 2011; Slopen, McLaughlin, & Shonkoff, 2014). Thus, understanding cortisol regulation in children and adolescents with PAE and ELA may provide an important window into both promising opportunities for intervention and possible physiological indices of both ELA and treatment gains.

The adverse effects of ELA parallel in many ways the adverse effects of PAE, both generally, and in particular, in relation to effects on HPA activity and regulation. Moreover, due to the high rates of ELA that frequently characterize the environment for children with PAE, it is often difficult, if not impossible, to separate the consequences of these early life insults. Thus, many studies evaluating the impact of PAE on cortisol regulation may be better characterized as studies of both PAE and environmental stress/adversity. However, few have explicitly focused on specific adversities in children with PAE, or on their combined impacts in older children and adolescents. This is the area where our work fills an important gap in the literature.

Based on the discussion above, we expected that the current cohort of children and adolescents with PAE would have high rates of ELA. Given that both ELA and PAE have demonstrated links with HPA activity and regulation, we sought to explicitly assess rates of ELA to determine if in fact this sample had experienced both impacts on development. Then, in the identified cohort of children and adolescents with PAE + ELA, we evaluated HPA function through assessment of cortisol activity, compared to that in typically developing children, by examining diurnal cortisol patterns. From the findings of Keiver et al. (2015) we postulated that dysregulation might be manifested by higher PM and possibly lower AM cortisol levels. We also sought to extend findings from the infant PAE-cortisol literature and the recent findings by Keiver et al. (2015) by exploring associations among cortisol regulation, ELA, adverse outcomes, and protective factors in children and adolescents with PAE + ELA. Based on evidence from other populations and on the fact that ELA might be acting on a stress system already sensitized by PAE, we hypothesized that the combination of PAE + ELA may be linked with increased HPA dysregulation, manifested as alterations in diurnal cortisol activity. Conversely, we expected that the presence of protective factors may be linked with more typical cortisol patterns.