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Cortisol awakening response in adults with attention deficit hyperactivity disorder: Subtype differences and association with the emotional lability

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Abstract
Cortisol awakening response (CAR) has been studied in children with ADHD, and some authors have reported morning cortisol differences among ADHD subtypes. Despite, only half of the children with ADHD continue to exhibit the disorder into adulthood, CAR has not been studied in adults so far. One hundred and nine adults with ADHD according to the DSM-IV criteria (46 inattentive and 63 combined) ranging in age from 18 to 55 years, and 27 healthy controls were included. Psychiatric and organic comorbidities were excluded. Salivary cortisol samples were obtained at 0, 30, 45 and 60 minutes after awakening. CAR was present in 84% of the healthy controls but in only 64% of the adults with ADHD (68% of the inattentive and 61% of the combined were CAR-positive). There were no significant differences in any of the morning cortisol measures between patients and controls or between the combined and inattentive subtypes of ADHD. Among the inattentive subtype but not in the combined patients, significant positive correlations were observed between the CAR and emotional lability (p=0.05), or self-concept (p=0.014) CAARS subscales, as well as with the cognitive impulsivity subscale of the Barratt impulsiveness scale (p=0.028). These results suggest that adults with ADHD exhibit normal cortisol responses upon awakening and

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thus cannot be defined in terms of hypo-arousal. Neurobiological differences between the combined and inattentive subtypes involving cortisol, are discussed.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects 8–12% of children and adolescents and 4–6% of adults (Biederman and Faraone, 2005). Thus, in half of the children with ADHD, the disorder persists into adulthood (Rasmussen and Gillberg, 2000). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), ADHD includes the following three subtypes: inattentive, hyperactive-impulsive, and combined. Only two symptom dimensions were used to define these three subtypes, i.e., inattention and hyperactivity-impulsivity as present in different life settings. Some authors have argued in favour of the presence of emotional symptoms in patients with ADHD (Retz et al., 2012), and Barkley noted the importance of impairments of self-emotional regulation as a core symptom of ADHD (Barkley, 2010; Jensen and Rosén, 2004). In this regard, the emotional lability (EL) subscale of the Conners' ADHD Rating Scale (CAARS) has been specifically associated with the emotional symptoms that characterize patients with ADHD, and this association is not explained by the presence of other psychiatric disorders (Vidal et al., 2014).

ADHD-related behavioural symptoms have been proposed to be associated with deficits of arousal or the ability to maintain optimal levels of arousal (Sonuga-Barke et al., 2010). Indeed, ADHD patients also suffer from sleep disturbances (Cortese et al., 2009), excessive daytime sleepiness (Lecendreux et al., 2000), afternoon increased hyperactivity (Antrop et al., 2002), and circadian heart rate changes with a trend toward high heart levels at specific times throughout the day (Imeraj et al., 2011). Arousal has been associated with the activity of the hypothalamic-pituitary-adrenal (HPA) axis, and cortisol is the main representative of the activity of this axis (Garde et al., 2011; Gore et al., 2006; Thorn et al., 2009). Cortisol is involved in a wide range of cognitive functions including focused attention, sustained effort and effortful thought (Dallman et al., 1993; Schulkin, 1999); all of these functions are difficult for patients with ADHD. Cortisol levels and their associations with physiological, cognitive and behavioural effects appear to be organized according to an inverted U-shaped curve in which medium cortisol levels are optimal, and high and low cortisol levels have adverse effects on behaviour and cognition and cause physiologically related issues (Beckwith et al., 1986; Lupien et al., 1997). Cortisol is also involved in behaviour; children who are described as energetic exhibit higher cortisol levels than those who are not (Granger et al., 1994). Extroverted children tend to exhibit greater cortisol increases than the more introverted children when starting a new activity such as a school course (Davis et al., 1999). There is also evidence for relationships between arousal (Dolcos et al., 2014; Lang et al., 1998), cortisol (Schulkin, 1999) and emotional regulation ability. Cortisol disturbances can at least partially explain the difficulties in the regulation of attention, behaviour and emotion mediated by neurobiological mechanisms in the prefrontal cortex (PFC) (Erickson et al., 2003).

The cortisol response at awakening (CAR) has been recognized as a potential biomarker of HPA axis function and psychosocial and health status (Thorn et al., 2009). The CAR is a specific increase in cortisol levels of approximately 50–75% that occurs within 30–45 min after awakening in the morning that can be measured in saliva samples (Pruessner et al., 2003, 1997; Wust et al., 2000) and can be detected in approximately 75% of healthy individuals. Some authors have reported that the CAR is a reliable predictor of consecutive daytime cortisol levels and can be considered to be a good measure of arousal (Edwards et al., 2001; Wilhelm et al., 2007). CAR has been studied in children with ADHD with and without comorbid disorders. Reduced cortisol awakening responses have been reported in a sample of hyperactive-impulsive 13-year-old children compared to age-matched controls; nevertheless, this study did not report the presence of comorbidities and hence their possible influences (Blomqvist et al., 2007). Some authors have explored the influences of the most frequent comorbidities in children with ADHD, i.e., oppositional deviant disorder (ODD) and conduct disorder (CD). Salivary cortisol is lower in ADHD children with ODD compared to healthy controls, and this deficit can be normalized with stimulant medication (Kariyawasam et al., 2002). Another study reported a blunted CAR in a group of children with ADHD and comorbid ODD compared to ADHD children ODD or CD and healthy controls (Freitag et al., 2009). Furthermore, Imeraj et al. explored CAR and daytime cortisol variations in children with and without ODD. No CAR differences were found between any of the patient groups and healthy controls; nevertheless, when evaluating cortisol profile across the day, the ADHD patients exhibited relative morning hypo-arousal and evening hiper-arousal, whereas the ADHD+ODD patients exhibited a steeper slope with relative morning hyper-arousal (Imeraj et al., 2011).

Because ADHD persists into adulthood in only half of affected children (Faraone and Biederman, 2005; Kessler et al., 2006), there is no direct evidence that the cortisol response in adults is the same as that in children. Additionally, a major limitation of previous studies that have assessed cortisol responses in ADHD is the presence of comorbidities that might have obscured the possible role of cortisol in ADHD. The aim of the present study was to investigate the CAR in adults with ADHD without comorbid disorders and to examine differences between the combined and inattentive subtypes. We also explored the associations between the cortisol response at awakening and the different subscales of the CAARS in both the inattentive and combined subtypes.