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Cortisol levels in children with Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

Regulation of the Hypothalamus–Pituitary–Adrenal axis (HPA-axis) and its end product cortisol differs among persons with certain psychiatric disorders when compared with controls. Some reports concern Attention-Deficit/Hyperactivity Disorder (ADHD) but findings are inconclusive. In this study we collected four saliva samples during a regular weekday in children, 6–17 years old, with ADHD ($n = 201$) and non-affected comparisons ($n = 221$). Saliva cortisol was measured with radioimmunoassay technique. Clinical data were collected for diagnostic information. Subtypes and severity of symptoms were determined using parental rating scales. Children with ADHD had lower saliva cortisol levels than comparisons at waking up Median = 9.1 versus 12.7 nmol/L ($p < .001$), 30 min later Median = 15.8 versus 20.1 nmol/L ($p < .001$) and before going to bed Median = 0.8 versus 1.0 nmol/L ($p = .015$). No difference was found for the afternoon sample. When the study group was split into three different age groups similar results were found only for children above 10 years of age. Subtype of ADHD or co-occurring symptoms did not affect the cortisol levels. Degree of severity of ADHD symptoms was not associated with cortisol levels in the study group, other than a weak negative correlation between the afternoon sample and hyperactivity symptoms. The low cortisol levels in children with ADHD may indicate a dysregulation of the HPA-axis, for instance a down-regulation or a phase delay of the diurnal curve. The low levels may be related to the under-arousal possibly underlying several of the core symptoms of ADHD.

1. Introduction

Regulation of the Hypothalamus–Pituitary–Adrenal axis (HPA-axis) and its end product cortisol differs among persons with certain psychiatric disorders when compared with controls (Tsigos and Chrousos, 2002). For instance, depression is associated with high levels of cortisol, possibly as an expression of impaired glucocorticoid-mediated feedback inhibition (Pariante and Lightman, 2008). A hyperactivation of the HPA axis has been reported not only for depression but also for obsessive–compulsive disorder (Gustafsson et al., 2008), panic disorder (Wedekind et al., 2000; Abelson et al., 2007) and anorexia nervosa (Lo Sauro et al., 2008). A decreased functioning of the HPA-axis has been associated with atypical depression (Tsigos and Chrousos, 2002), chronic fatigue syndrome (Roberts et al., 2004; Papadopoulos and Cleare, 2011; Tak et al., 2011), posttraumatic stress disorder (PTSD) (Yehuda, 1998; Heim et al., 2000) and fibromyalgia (Griep et al., 1998; Riva et al., 2010). Several reports concern Attention-Deficit/Hyperactivity Disorder (ADHD), a neurobehavioral developmental disorder with three subgroups characterized by predominantly symptoms of inattention (ADHD-I), hyperactivity/impulsiveness (ADHD-HI) or both types, "combined" (ADHD-C).

However, the results are not conclusive; both hyper- and hypofunctioning have been reported as well as no differences in comparisons with children without ADHD-symptoms (for a short review, see below). Hypothetically, an association between a down-regulated HPA axis and ADHD fits with theories that regard ADHD as a consequence of under-arousal (Fairchild, 2010). One such theory is the optimal stimulation theory (Zentall and Zentall, 1983) which suggests that the manifestations of ADHD can be seen as expressions of increased activity which aims at promoting arousal, e.g. through shifts in attention, talking, seeking stimulation, risk-taking or aggressive behavior (Zentall, 2005).

The secretion of cortisol follows a diurnal cycle, characterized by high levels on awakening, a further increase during the morning and a gradual decrease over the day until midnight (Tsigos and Chrousos, 2002). Abnormalities of the HPA axis in children with ADHD were originally suggested in 1993 by Kaneko et al. who found that a normal diurnal cortisol rhythm (defined as maximum

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levels in the morning and minimum levels in the evening) was less frequent in children with ADHD than in (adult) controls. They also reported that the children with ADHD less frequently than the controls responded with suppression when exposed to dexamethasone, a synthetic steroid with capacity of suppressing the secretion of ACTH (dexamethasone suppression test [DST]) (Slater et al., 1962). Since then studies of cortisol have focused either on a dysfunctional circadian rhythm or an impaired reactivity after DST or exposure to an experimental stressor. Further, studies have focused on cortisol levels in relation to severity of ADHD symptoms, different diagnostic subtypes or co-morbidity.

Several authors have reported an association between low cortisol levels and either hyperactivity (Kaneko et al., 1993; Blomqvist et al., 2007; Ma et al., 2011) or ADHD symptoms in general (Scerbo and Kolko, 1994; King et al., 1998). Others have reported low cortisol levels in children with co-morbid oppositional defiant disorder (ODD) (van Goozen et al., 1998; Kariyawasam et al., 2002; Freitag et al., 2009) or disruptive behavior (Hastings et al., 2009). In contrast several studies have failed to demonstrate any relation between cortisol levels and ADHD in general (Pesonen et al., 2011; Wang et al., 2011), for attention (Sondeijker et al., 2007), for hyperactivity (Hatzinger et al., 2007) and for ADHD with aggressive behavior (Schulz et al., 1997). Studies on stress reactivity display a similar ambiguity. A blunted response has been associated with ADHD (King et al., 1998; McCarthy et al., 2011), hyperactivity (Hong et al., 2003; van West et al., 2009), inattentive problems (Randazzo et al., 2008; Pesonen et al., 2011) and ODD co-morbidity (Snoek et al., 2004; Hastings et al., 2009). Contrarily, others have not found a decreased cortisol response in children with ADHD in general (Jansen et al., 1999; White and Mulligan, 2005; Christiansen et al., 2010) or with hyperactivity (Hatzinger et al., 2007).

In summary, findings reported on ADHD and cortisol levels are inconclusive. This may reflect methodological limitations such as small samples (only three studies with $n > 100$), varying – and not rarely vague – diagnostic routines, comparison groups with unknown "contamination" of individuals with ADHD and unsatisfactory control of sampling times. Furthermore, only a few studies have captured the morning cortisol levels by collecting samples when awakening and soon thereafter. Thus, in the present study we aimed at investigating the diurnal levels of saliva cortisol in school aged children (6–17 years of age) with ADHD and age matched healthy comparisons also taking severity, subgroup and co-occurring symptoms into consideration.

2. Method

2.1. Procedure

Children/adolescents (6–17 years of age) of the study group were recruited from four child psychiatry outpatient units in three Swedish counties where the ADHD-diagnosis had been verified by neuropsychiatric assessment. Written project information was presented at a regular examination or – in one county – by mail to the parents and to the child (an age-adapted version). After written informed consent from parents (and child when ≥15 years of age) a questionnaire about current medication (ADHD-medication as well as any other medication), tubes for saliva samplings and instructions were mailed to the family. Clarifications were given by phone. Information about diagnosis/es and symptom ratings (Swanson, Nolan and Pelham ADHD symptom rating scale [SNAP-IV] and the Five to Fifteen [FTF] parental questionnaire, see below) was collected from the medical record. All data were recoded and all identifying information was destroyed, thereby implementing total anonymity.

For the comparison group, children of the same ages and from schools in the same areas as the study persons were invited by mail or parental meetings, depending on the decision of the principal. In the written information we clarified that children with verified or suspected ADHD should not participate. When the informed consent from parents (and child when ≥15 years of age) was returned, the following material was mailed to the family: SNAP-IV, questions about current medication, tubes for saliva sampling and sampling instructions. Clarifications were given by phone. The data were made anonymous as described above. The study was approved by the Regional Ethical Review Board in Uppsala, no. 2009/034 and in accordance with the latest version of the Declaration of Helsinki. Informed consent of all participants was obtained after the nature of the procedures had been fully explained.

2.2. Symptom questionnaires (parental ratings)

Parental ratings on SNAP-IV were used for estimating the severity of ADHD symptoms, for identifying subtypes of ADHD (ADHD-I, ADHD-HI, ADHD-C), for identifying co-morbidity of ODD and for excluding comparisons with high ADHD ratings (Swanson et al., 2001). The version applied has 30 items (9 for inattention, 9 for hyperactivity/impulsivity, 8 for ODD, 4 control questions), scored by parents and teachers on a 4-point scale: 0 for "not at all", 1 for "just a little", 2 for "quite a bit" and 3 for "very much". It has been psychometrically tested in a Northern American sample and has demonstrated "acceptable internal consistency and item selection, and a factor structure consistent with the two-factor solution of ADHD symptoms, and a third ODD factor" (Bussing et al., 2008). Normative data for Swedish children are not available. However, intercultural similarities and the firm basis in the DSM IV-criteria motivated this choice. The overall Cronbach's Alpha was .97 in the study group and comparison group together. Similar results were found in both groups. The alpha varied between .80 and .92 for the subscales. ODD was defined as at least four items scored as "quite a bit" or "very much".

Parental ratings on the Five to Fifteen (FTF) questionnaire were applied for identifying co-occurring symptoms in the study group only. This instrument has been developed in the Nordic countries and covers concomitant problems of ADHD (Kadesjö et al., 2004). It comprises 181 three-graded statements, arranged into eight domains (memory, learning, language, executive functions, motor skills, perception, social skills and emotional/behavioral problems) and most domains can be further divided into sub-domains. We selected data from sub-domains reflecting symptoms related to psychiatric disorders with an association to HPA-axis dysfunction: social skills (autism spectrum, 27 items), obsessive–compulsive symptoms (OCD, 8 items), internalizing emotional problems (depression/anxiety, 12 items) and externalizing emotional problems (ODD/conduct disorder, 13 items). Scores from these sub-domains were used in analyses on the association between cortisol levels and co-occurring psychiatric symptoms. FTF has acceptable to excellent test-retest reliability and internal consistency (Kadesjö et al., 2004). In our study group the Cronbach's Alpha varied between .73–.92 for relevant sub-domains. Validity of FTF has (for relevant parts) been ascertained by comparisons with clinically diagnosed children (Trillingsgaard et al., 2004).

2.3. Subjects

Descriptive data on subjects are presented in Table 1.

2.3.1. Study group

After exclusion of eight children reporting saliva sampling during a weekend or a holiday the study group amounted to 201