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ORIGINAL ARTICLE

Reduced Salivary Cortisol in Children with Comorbid Attention Deficit Hyperactivity Disorder and Oppositional Defiant Disorder

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Abstract

OBJECTIVES: There is growing interest in the role of the hypothalamic-pituitary-adrenal (HPA) axis in neuropsychiatric disorders and there is some evidence that the HPA axis may be underfunctional in behaviorally disturbed children. However, co-morbidity is common in childhood neuropsychiatric disorders. Stimulant medication is widely used in the treatment of Attention-deficit hyperactivity disorder (ADHD) and can increase cortisol secretion when given acutely. We therefore set out to determine the whether salivary cortisol would be reduced in a group of children with ADHD/ODD (Oppositional-defiant disorder) and to examine the effect of stimulant medication on any such relationship. **DESIGN**: Salivary cortisol was determined in thirty-two children with co-morbid ADHD and Oppositional-defiant disorder (ODD) according to DSM-IV criteria, compared to twenty-five healthy controls of similar age and ethnic background. Data were analysed according to prescription of stimulant medication in the patient group. **RESULTS**: Salivary cortisol was significantly lower in the ADHD/ODD group than in the controls. Further analysis revealed that this reduction was restricted to the subgroup of patients not prescribed stimulant medication. **CONCLUSIONS**: The results support the possibility of a dysfunction of control of the HPA axis in these behaviorally disturbed children. A reduction in salivary cortisol could reflect underarousal, an elevated threshold for detection of stressors or a subsensitivity of the HPA axis itself. It remains to be determined whether the ability of stimulant medications to negate the apparent deficit in cortisol secretion in these ADHD/ODD patients is an unrelated consequence of increased dopamine release or a reflection of their therapeutic benefit. The use of stimulant medication for co-existing ADHD should be taken into account in future studies of cortisol in behaviorally disturbed children.

Introduction

There is growing interest in the potential role of the hypothalamic-pituitary-adrenal (HPA) axis in neuropsychiatric disorders [1,2] and there is some evidence that behaviorally disturbed children may exhibit under-functionality of the HPA axis. Salivary cortisol correlates closely with plasma free cortisol and it is well established that salivary cortisol levels reflect cortisol secretion [3,4]. In a study of boys with Oppositional-Defiant Disorder (ODD) [5] it was reported that baseline levels of salivary cortisol were lower than in a comparison group of normal controls, but this difference only reached statistical significance following removal of outliers from the ODD group and the two groups did not differ significantly in response to stress. Furthermore, within a group of children referred for disruptive behavior, those with persistent aggression showed lower single-point concentrations of salivary cortisol and a smaller stress-induced elevation than those without this feature [6]. Similarly, following placement of scalp electrodes, children with substance-abusing fathers had lower single-point salivary cortisol than those without [7]. Children with Attention-deficit hyperactivity disorder (ADHD) persisting over two years exhibited reduced single-point salivary cortisol and cortisol stress response to neuropsychiatric testing compared to a group with a more transient form of the disorder [8].

There is a high degree of co-morbidity among neuropsychiatric disorders of childhood [9,10]. For example, the incidence of ODD in ADHD has been variously recorded as 43–93% [9]. The beneficial effect of stimulant medications in ADHD lends support to the hypothesis that some form of under-arousal is implicated in ADHD [11,12]. However, these medications can also elevate circulating cortisol, at least when administered acutely [13].

We therefore set out to determine the whether single-point determinations of salivary cortisol would be reduced in a group of children with ADHD/ODD visiting Diana Princess of Wales Children's Hospital for follow-up care, compared with healthy children of similar age, sex and ethnic background, and examine the effect of stimulant medication.

Methods

32 children with a co-diagnosis of ADHD and ODD, according to DSM-IV criteria [10], and attending Diana Princess of Wales Children's Hospital, Birmingham, UK for follow-up care, were recruited as subjects; while 25 healthy volunteers were recruited from local schools as controls. Neuropsychiatric disorders were exclusion criteria for the control group and steroid-containing medications were exclusion criteria for both groups. The presence of intercurrent infectious or physical disease was excluded in both patient and control groups.

A 2ml sample of saliva was collected from each child, without any artificial aid to saliva production, into a polypropylene container between 14.00 and 17.00 h. Both groups donated saliva samples in a familiar environment. Since cortisol secretion shows a seasonal variation [14], the salivary samples from patients and controls were taken over a restricted period of 2 months (February and March). Saliva samples were frozen at –70°C until cortisol concentrations were assayed by radioimmunoassay [15].

Data were analysed by Analysis of Variance (SPSS version 10); Dunnett's T3 was used as the *post-hoc* test for multiple comparisons, since Levene's test indicated significant non-homogeneity of variance. Alpha was set at 0.05.

The study was approved by South Birmingham NHS Trust Ethical Committee, and Birmingham Local Educational Authority approval was obtained for recruitment of the healthy volunteers.

Results

The 32 ADHD/ODD patients (three female, mean age 10.6 ± 0.6 (s.e.m.) years) were all of ADHD combined type. Further diagnoses were: Conduct disorder, 6; Chronic motor tics, 3; Tourette syndrome, 18; Obsessive compulsive disorder/behaviors, 4; Trichotillomania, 3; Learning disorder, 4. No child from an ethnic minority attended the Diana Princess of Wales Children's hospital in Birmingham for follow-up care during the study period. The 25 healthy volunteers (three female, none from an ethnic minority) had a mean age of 11.3 ± 0.6 years (not significantly different from ADHD/ODD group, $p>0.05$). There were no significant differences in salivary cortisol between the two months of the study ($F_{(1,56)} = 0.08$; $p>0.05$).

Salivary cortisol was significantly ($p<0.05$) lower in the ADHD/ODD group (2.69 ± 0.2 nMol/L) than in the healthy controls (3.52 ± 0.26 nMol/L). The 18 patients who were stimulant-free exhibited a highly significant ($p < 0.01$) reduction in salivary cortisol compared with the healthy controls, while the 14 ADHD patients prescribed stimulants (D-amphetamine or methyl-phenidate) exhibited salivary cortisol concentrations not significantly different from the healthy controls (figure 1). There was no significant difference in salivary cortisol between the two stimulant medications ($p>0.7$).

Discussion

This study demonstrates significantly reduced salivary cortisol in comparison to healthy controls, in

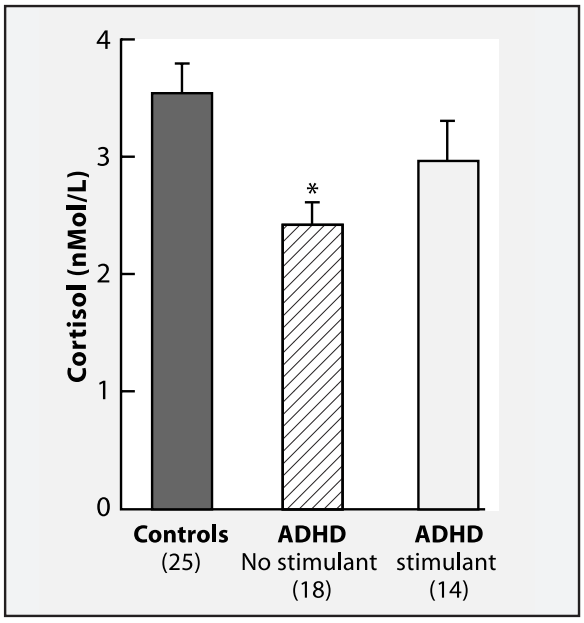

Figure 1: Salivary cortisol in children with ADHD compared with healthy controls. The ADHD group was divided by prescription of stimulant medication. Vertical bars represent standard error of the mean. * p<0.01 compared with control group (Dunnett's T3 *post hoc* test following 1-way ANOVA ($F(2,56)$ 4.51, $p < 0.05$); there were no other significant differences between groups).

children with ADHD/ODD, in the absence of an imposed stress. This effect was localized to the subgroup of children who had not been prescribed stimulant medication. This observation supports the possibility of a disturbance in the HPA axis in these behaviorally disturbed children. Previous studies suggest reduced cortisol responsiveness to stress in children lacking the ability to exhibit age-appropriate inhibition of impulsive and/or aggressive behavior [5-8]. In contrast, relatively higher salivary cortisol levels have been detected in children reported as shy and behaviorally inhibited, compared with children having age appropriate behavior [16]. Taken together with the present finding, these reports suggest that both lower and higher cortisol responsiveness can be associated with behavioral problems.

The etiology of neuropsychological disorders such as ADHD and ODD is not yet known. The hypothesis that some form of underarousal is implicated in ADHD is supported by the beneficial effects of stimulants [11,12] but has found little support from brain imaging studies [17–20]. Cortisol is the prototypical stress hormone and stress-induced cortisol elevation is likely to be a major contributor to non-basal cortisol secretion [21,22]. The relationship between stress and arousal is, however, difficult to untangle, especially as a distinct increase in cortisol is seen on awakening, superimposed on the circadian rhythm [23]. Thus a reduction in salivary cortisol could reflect underarousal, an elevated threshold for detection of stressors or a subsensitivity of the HPA axis itself. Further studies are warranted to explore whether the observed changes in salivary cortisol are maintained over the circadian secretion cycle, particularly with respect to basal secretion.

Single acute doses of stimulants such as D-amphetamine or methylphenidate have been shown to increase circulating cortisol, an effect that appears to be related to the ability of these substances to trigger dopamine release in the CNS [13]. In the present study, stimulant medication abolished the reduction in cortisol seen in the ADHD/ODD group. Cortisol was relatively higher in patients prescribed stimulants than in those without but this did not reach statistical significance, perhaps due to tolerance developing on sustained medication. It remains to be determined whether the ability of stimulant medications to negate the apparent deficit in cortisol secretion in these ADHD/ODD patients is an unrelated consequence of increased dopamine release or a reflection of their therapeutic benefit. The use of stimulant medication for co-existing ADHD should be taken into account in future studies of cortisol in behaviorally disturbed children.

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