Saliva Cortisol and Response to Dexamethasone in Children of Depressed Parents

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Background: *Major depression (MDD) is heritable, and children of depressed parents are at higher risk for the development of depression. However, depression in a parent might also act as a stressor leading to increased activation of neuroendocrine stress circuits. To address this question we examined saliva cortisol in children whose parents have a history of MDD.*

Methods: *We recruited 15 families with one parent with MDD (26 prepubertal children) and 16 control families without history of parental MDD (32 prepubertal children). All parents and children underwent Structured Clinical Interview for DSM-IV and Kiddie Schedule For Affective Disorders And Schizophrenia interviews, respectively. Families were asked to collect morning, afternoon, and bedtime saliva samples for 4 days for 2 weeks. At bedtime of the 3rd day, dexamethasone was administered. Two doses, standard and low, were used in each family.*

Results: *The majority of children demonstrated no psychiatric diagnosis. Children with MDD parents showed higher cortisol basally and higher cortisol after both 25 mg and 5 mg dexamethasone. However, this effect occurred predominantly in children whose parents were currently depressed. There were strong correlations for cortisol between parents and children (*r *= 52 in depressed;* r *= 499 in control).*

Conclusions: *Elevated cortisol and impaired feedback seemed to reflect an environmental effect of MDD in a parent.*

Key Words: Stress, hypothalamic-pituitary adrenal axis, major depression, high-risk offspring, glucocorticoid feedback, cortisol

The finding that depression is familial has spurred controversy over the genetic versus environmental contributions to these findings. Recent conceptualizations have moved toward integrating these views and realizing that depression in a parent can act as a stressor in a developing child and that this stressor might interact with underlying vulnerability factors to produce long-term effects on children including increased risk for depression (Kendler et al 2002). Studies of high-risk offspring have been pursued to determine what factors might predispose to future depression in childhood or adulthood.

One of the most robust biological changes associated with major depression (MDD) is increased cortisol secretion (Carroll et al 1976; Rubin et al 1987; Young et al 2001). This increased cortisol secretion has been associated with insensitivity to dexamethasone feedback (Carroll et al 1981). Cortisol is a marker for activation of central stress systems, particularly corticotropin releasing hormone (CRH), which might be elevated in children under stress such as that experienced when a parent is depressed. Although increased cortisol in depression has been regarded as a state marker, this conclusion is based upon the normalization of cortisol after treatment with antidepressants (Albala et al 1981; Greden et al 1983; Heuser et al 1996). However, data demonstrating direct effects of antidepressants on the hypothalamic pituitary adrenal (HPA) axis have called into question these findings (Brady et al 1991; Holsboer and Braden 1996; Lopez et al 1998; Pariante et al 2001). Several recent studies have found elevated saliva cortisol in euthymic patients not receiving medications, suggesting that elevated cortisol might be persistent or even a risk factor for MDD (Bhagwagar et al 2003; Young and Breslau 2004; Young et al 2000).

Studies of high-risk adults and adolescents have found more variable morning cortisol in those who subsequently develop MDD (Goodyer et al 2000; Harris et al 2000). Lupien et al (2000) found higher cortisol levels in children of depressed mothers. Essex et al (2002) reported on a longitudinal sample and found higher cortisol cross-sectionally in children under current stress, but longitudinal analysis revealed that it was children with both early stress during infancy and current stress that demonstrated the increased cortisol. Halligan et al (2004) found higher and more variable morning cortisol in children whose mother had experienced postpartum depression. Consequently, the literature suggests that children exposed to maternal depression might demonstrate higher cortisol, that the effect might persist during childhood, and that higher and variable cortisol might be a predictor of subsequent depression. However, no studies have examined the dexamethasone feedback in children at high risk for depression. The current study was undertaken to look for possible effects of maternal or paternal depression on children. We sampled saliva cortisol in the morning and evening on 6 basal days over 2 weeks and also after two doses of dexamethasone.

Methods and Materials

Subjects

The studies were conducted between 1997 and 2000. All studies were approved by Weill Medical College of Cornell University and University of Michigan institutional review boards. All adults gave informed consent and children gave assent. Families in which one parent had a history of depression were recruited by advertisement or from cases seen in the University of Michigan Depression Clinic. In some cases, the families had responded to advertisements for normal families. A Structured Clinical Interview for DSM-IV (SCID) was conducted on both parents, and a Kiddie Schedule For Affective Disorders And Schizophrenia (K-SADS) interview was conducted on the children. For control families, we required that both parents be interviewed, even if the parents were no longer married, to

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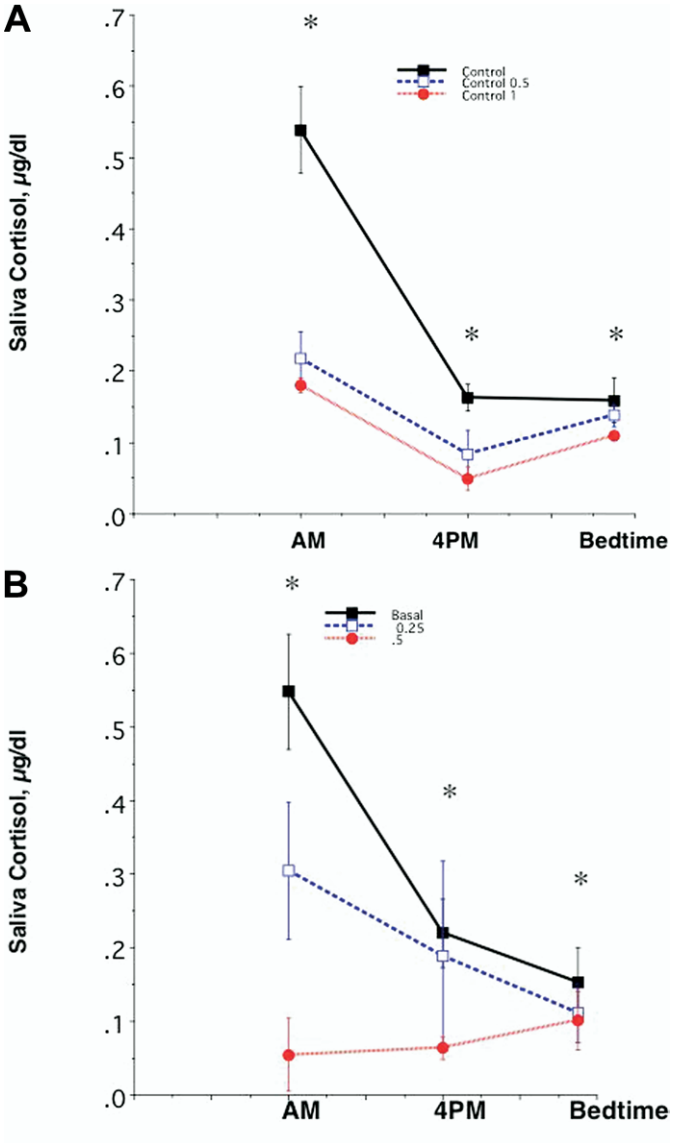

Figure 1. Basal and post-dexamethasone saliva cortisol levels in control adults **(A)** and control children **(B)**. In adults the doses of dexamethasone were .5 mg (control .5) and 1 mg (control 1). In children the doses of dexamethasone were 25 mg (.25) and 5 mg (.5). Although both groups show significant suppression of saliva cortisol with dex, in adults saliva cortisol after 5 mg was not significantly different than after 1 mg, whereas in children saliva cortisol was significantly different with .25 mg and 5 mg dex. Asterisks indicate significant differences.

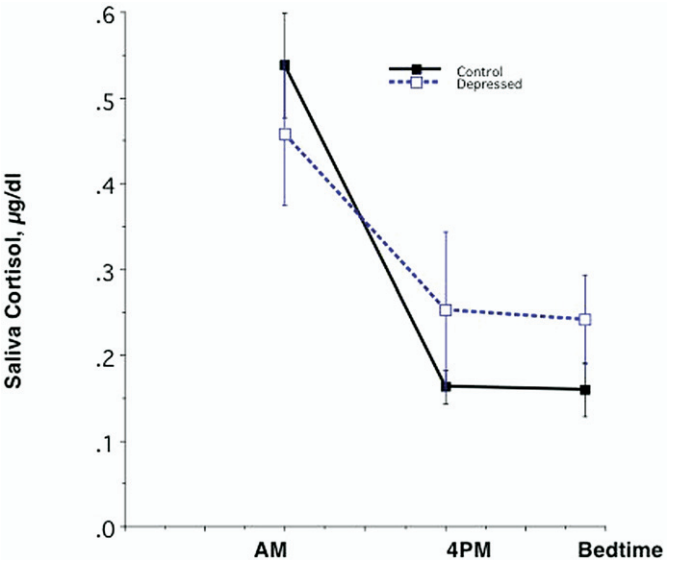

Figure 2. Effect of depressive diagnosis on saliva cortisol in parents compared with normal controls parents. The parents with lifetime depression show higher cortisol in PM, although this is not significant.

assure that neither parent had depression. In the families with a depressed parent, if the spouse was unavailable/divorced we did not interview the spouse. The K-SADS was administered to the parent and child separately, if children were able to answer questions about symptoms, and then the results discussed in a conference between parent and children. A general measure of family coping (General Scale of Family Assessment; Skinner et al 1995) was also collected. Normal families were recruited by advertisement. Both control parents and children had to be free of psychiatric diagnosis as assessed by the SCID–Non-Patient and K-SADS. In addition, no first degree relative of the control parents could have a history of MDD. In both normal and depressed families, all prepubertal children over the age of 7 were included in the study. Prepubertal status was determined by age and by questionnaire given to parent or child about developmental sexual characteristics.

Saliva Sampling Paradigm

All subjects were instructed to collect saliva samples within 45 min of awakening and within 45 min of bedtime for 3 consecutive days. The 3rd day also included a 4:00 PM saliva sample. At bedtime of the 3rd day (and after evening salivary cortisol was collected), subjects took dexamethasone (dex); either low dose or high dose, followed by saliva sample collection within 45 min of awakening, at 4:00 PM, and bedtime the following day. The following week, the same procedure was repeated with substitution of the alternate dose of dex. On the evening of dex administration, all families received a reminder call from the research assistant. The order of dex doses was randomized across families, but all members of the family received the same order (i.e., low dose first or high dose first). In children, low dose was .25 mg and high dose was .5 mg dex. In adults, low dose was .5 mg and high dose was 1 mg dex. All studies were conducted on weekdays/school days, to maintain "normal" circadian rhythm and similar sampling times for cortisol. Saliva samples were collected in Salivettes (Starstedt, Newton, North Carolina). Samples collected at Cornell were shipped frozen on dry ice to Michigan for assay. All samples were assayed with DPC (Los Angeles, California) Coat-a-Count cortisol kits following the manufacturer's direction for saliva assays. In some cases a parent other than the depressed parent was the parent contributing the saliva samples. Thus, of the 15 families with a parent with depression, 10 adults with a history of depression contributed samples, whereas saliva samples from 5 of the families were from their well partners. Of these 10 adults, 4 had active MDD at the time of the study. Four of the parents with MDD were receiving antidepressant medications; 2 of these were currently depressed. In all actively depressed parents, the mother was the depressed parent. In the total sample, 2 of the parents with depression were fathers whereas 13 were mothers.