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Serotonin transporter polymorphism predicts waking cortisol in young girls

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Summary Major Depressive Disorder (MDD) is one of the most prevalent and costly of all psychiatric disorders. The hypothalamic pituitary adrenal (HPA)-axis, which regulates the hormonal response to stress, has been found to be disrupted in depression. HPA dysregulation may represent an important risk factor for depression. To examine a possible genetic underpinning of this risk factor without the confound of current or lifetime depression, we genotyped 84 never-disordered young girls, over a third of whom were at elevated risk for depression, to assess the association between a polymorphism in the promoter region of the serotonin transporter (5-HTT) gene and diurnal variation in HPA-axis activity. This 5-HTT-linked polymorphic region (5-HTTLPR) has been previously found to interact with stress to increase risk for depression. We found 5-HTTLPR to be significantly associated with diurnal cortisol levels: girls who were homozygous for the short-allele had higher levels of waking (but not afternoon or evening) cortisol than did their long-allele counterparts. This finding suggests that genetic susceptibility to HPA-axis dysregulation, especially apparent in levels of waking cortisol, is detectable in individuals as young as 9 years of age.

1. Introduction

Major Depressive Disorder (MDD) is among the most prevalent and costly of all psychiatric disorders. About 16% of the general population will experience an episode of MDD in their lifetimes, and up to two-thirds of these individuals will experience recurrent episodes (Eaton et al., 2008; Kessler et al., 2003). Given the extraordinary societal costs and the personal burden that are associated with this disorder (e.g., Greenberg et al., 2003), it is critical that we identify and elucidate factors that place individuals at elevated risk for the development of MDD.

In this context, a number of investigators have examined the serotonin system in depression (see Thase, 2008, for a review). Most recently, spurred in part by the effectiveness of selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression, researchers have begun to examine the role of the genetics of the serotonin system in placing individuals at elevated risk for this disorder (Levinson, 2006). Specifically, several investigators have found the serotonin transporter gene (5-HTT) linked polymorphic region (5-HTTLPR) to interact with major life stress to predict the

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onset of MDD (e.g., Caspi et al., 2003; Kendler et al., 2005); when exposed to stress, individuals who are homozygous for the short-allele (SS individuals) are more likely to develop depression than are individuals with one or two long alleles (SL or LL individuals). The involvement of life stress in this interaction is consistent with a large literature implicating stress in the onset of depression (Monroe et al., 2008) and underscores the importance of investigating stress reactivity in people who are vulnerable to the development of this disorder. In fact, depressed individuals have been found to be characterized by dysfunctional activity of the hypothalamic pituitary adrenal (HPA)-axis, which regulates hormonal responses to stress. More specifically, depressed persons exhibit elevated levels of cortisol (Gillespie and Nemeroff, 2005). In fact, hypercortisolemia is associated not only with increased severity of depression (Whiteford et al., 1987), but with hippocampal changes and damage (McEwen, 1999; Sapolsky, 2001) and with increased risk for cardiovascular disorders (Weber-Hamann et al., 2002).

Recently, Gotlib et al. (2008) found that the same polymorphism in 5-HTTLPR that interacts with life stress to predict the onset of depression is associated with increased cortisol response to an acute laboratory stressor. It is important to note that while the HPA-axis produces cortisol in response to acute stressors, HPA-axis activity also follows a diurnal rhythm, with cortisol levels typically rising with morning waking and declining throughout the day (Posener et al., 1996; Born et al., 1999). Anomalous diurnal patterns of cortisol secretion may indicate systemic dysregulation in HPA-axis feedback; indeed, investigators have documented elevated levels of waking cortisol in individuals diagnosed with MDD (Young, 2004; Bhagwagar et al., 2005). Perhaps not surprisingly given the association of serotonin with depression (cf. Thase, 2008), evidence from both human and animal studies indicates that the regulation of HPA-axis function involves the serotonergic system (e.g., Porter et al., 2004; Linthorst, 2005). Although Gotlib et al. (2008) recently demonstrated that the 5-HTTLPR polymorphism is associated with cortisol response to an acute stressor, it is not known whether the effects of the 5-HTTLPR polymorphism are confined to stress reactivity cortisol, or whether this polymorphism would also be associated with differential systemic HPA-axis function. The present study was designed to examine whether 5-HTTLPR polymorphisms are related to diurnal cortisol production.

We predicted that homozygous short-allele carriers would be characterized by higher levels of diurnal cortisol than would heterozygous participants, with homozygous long-allele carriers producing the lowest levels of diurnal cortisol. Moreover, given recent findings that depression is associated with increased levels of waking cortisol in particular (Bhagwagar et al., 2005), we predicted that the genetic effects on cortisol production would be strongest during the morning, immediately after waking. Finally, because we wanted both to examine the relation between 5-HTTLPR polymorphisms and diurnal cortisol without the confound of current or past depression and to have a sufficient number of homozygous and heterozygous short- and long-allele participants, we assayed diurnal cortisol from two groups of participants with no current or past episodes of depression: daughters of mothers who had no history of depression, and daughters of mothers who had a history of recurrent depression during their daughters' lifetime. We examined only female participants both because of the higher prevalence of MDD in females than in males (Kessler et al., 2003) and to increase the homogeneity of the sample.

2. Method

2.1. Participants

Participants were 84 girls between the ages 9 and 14 who had no current or past DSM-IV Axis I disorder. Fifty-three of these girls were daughters of mothers who also had no current or past Axis I disorder (low risk for depression), and 31 were high-risk daughters of mothers who had a history of recurrent episodes of Major Depressive Disorder during their daughters' lifetime (high risk for depression); all daughters in the study came from different families. Participants were recruited through internet and print advertisements in the local community or through the Department of Psychiatry and Behavioral Sciences at Stanford University. The mothers' responses to a telephone interview provided initial selection information. This phone screen established that both mothers and daughters were fluent in English and that daughters were between 9 and 14 years of age. The telephone interview was also used to identify mothers who were likely either to have no psychiatric history or to meet criteria for recurrent depression during their daughter's lifetime, and daughters who were likely to have no past or current psychiatric disorder. Those mother and daughter pairs who were considered likely to be eligible for participation were invited to come to the laboratory for more extensive interviews.

2.2. Assessment of depression and psychopathology

At the interview session, trained interviewers assessed the diagnostic status of daughters by administering the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL; Kaufman et al., 1997) separately to the daughters and to their mothers (about the daughters). The full interview, assessing current and lifetime diagnoses for affective, psychotic, anxiety, behavioral, substance abuse, and eating disorders was administered. Due to time constraints and the fact that all our participants were female, the Tic Disorders and ADHD screeners were not administered (both of these disorders are more prevalent in boys: Gadow et al., 2002). The K-SADS-PL has been shown to generate reliable and valid child psychiatric diagnoses (Kaufman et al., 1997). A different interviewer administered the Structured Clinical Interview for the DSM-IV (SCID; First et al., 1997) to the mothers. The SCID has demonstrated good reliability for the majority of the disorders covered in the interview (Skre et al., 1991; Williams et al., 1992). Both K-SADS-PL and SCID-I interviewers had previous experience with administering structured clinical interviews and were trained specifically to administer these interviews. To assess interrater reliability, an independent trained rater who was blind to group membership evaluated 30% of the SCID and K-SAD-PL interviews by randomly selecting audiotapes of equal numbers of at-risk and control pairs. In all cases, diagnoses of former depressive episodes in