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Salivary cortisol in unaffected twins discordant for affective disorder

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Abstract

Dysfunction in the hypothalamic–pituitary–adrenal (HPA) axis has been proposed as a biological endophenotype for affective disorders. In the present study the hypothesis that a high genetic liability to affective disorder is associated with higher cortisol levels was tested in a cross-sectional high-risk study. Healthy monozygotic (MZ) and dizygotic (DZ) twins with (High-Risk twins) and without (Low-Risk twins) a co-twin history of affective disorder were identified through nationwide registers. Awakening and evening salivary cortisol levels were compared between the 190 High- and Low-Risk twins. The 109 High-Risk twins had significantly higher evening cortisol levels than the 81 Low-Risk MZ twins, also after adjustment for age, sex, and the level of subclinical depressive symptoms. No significant difference was found in awakening cortisol levels between High-Risk and Low-Risk twins. In conclusion, a high genetic liability to affective disorder was associated with a higher evening cortisol level, but not with awakening cortisol level. Future prospective family, high-risk and twin studies are needed to decide whether abnormalities in the HPA axis can be identified as an endophenotype of affective disorder.

Keywords: Cortisol; Mood disorders; High-risk study

1. Introduction

Cortisol is the end product of the hypothalamic–pituitary–adrenal (HPA) axis. Corticotrophin-releasing factor (CRF) from hypothalamus paraventricular nucleus stimulates secretion of adrenocorticotrophic hormone (ACTH) in the pituitary and ACTH stimulates the production of cortisol in the adrenals. Through a negative feedback mechanism, cortisol inhibits production of ACTH and CRF, thereby inhibiting its own secretion (Sapolsky et al., 1986; Young, 2004). The HPA axis is involved at several levels in affective disorder, and increased secretion of cortisol is observed in a proportion of patients with affective disorder (Dinan, 1994; Christensen and Kessing, 2001; Nemeroff and Vale, 2005). It is unknown whether abnormalities in the HPA system are present before the onset of affective disorders and whether these abnormalities are associated with a high genetic liability to affective disorder. It is also unknown whether an altered HPA axis physiology is part of an individual's vulnerability to psychopathology, and

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there is a lack of studies concerning the prospective value of HPA axis dysregulation (Rosmalen et al., 2005).

Dysfunction in the HPA axis has been proposed as a biological endophenotype for genetic studies (Hasler et al., 2004). An endophenotype should fulfil the following criteria: it is associated with illness in the population; it is heritable and primarily state independent; within families, the endophenotype and the illness co-segregate, and the endophenotype found in family members is found in non-affected family members at a higher rate than in the general population (Gottesman and Gould, 2003). Prospective studies, measuring cortisol before the onset of affective disorder, may provide information on whether the dysfunction in the HPA axis is related to genetic factors and represents endophenotypes between genes and the disorders. Therefore, assessment of first-degree relatives of patients with affective disorders may provide a powerful design to investigate the biological vulnerability in unipolar and bipolar disorders (Sobczak et al., 2000).

Few studies have investigated the HPA axis in non-affected family members of patients with affective disorders. Three studies included first-degree relatives of patients with depression, and all found higher cortisol levels in the morning than in participants who had no personal history of affective disorder and no reported affective episodes in a first-degree relative (Lupien et al., 2000; Halligan et al., 2004; Mannie et al., 2007). In a recent study of unaffected offspring of bipolar patients, no differences were seen in the cortisol level between offspring and control persons (Deshauer et al., 2006). In contrast, two studies of adolescent offspring of parents with bipolar disorder showed evidence of increased daytime basal HPA functioning with normal reactivity to psychosocial stress (Ellenbogen et al., 2004; Ellenbogen et al., 2006).

Kendler et al. (1995) were the first to describe a study design that identified twins in four categories of risk by crossing zygosity with family history of affective disorder. This design provides an opportunity to investigate a sample with a great variation in the genetic liability to affective disorder. In the present study, healthy MZ and DZ twins with and without at least one first generation family history of affective disorder were identified through nationwide registers. Accordingly, the following four groups were identified: 1) Twins at high risk of development of affective disorder (MZ twin, co-twin affected). 2) Twins at moderate risk of development of affective disorder (DZ twin, co-twin affected). 3) Twins moderately protected against development of affective disorder (DZ twin, co-twin unaffected). 4) Twins at low risk of development of affective disorder (MZ twin, co-twin unaffected). The High-Risk twins included in this study show higher rates of subclinical affective symptoms (Christensen et al., 2007), signs of discrete cognitive dysfunction (Christensen et al., 2006) and a higher neuroticism score, but the higher neuroticism score interacts with other predictors of affective disorder: female gender, minor psychopathology and recent adversity (Vinberg et al., 2007), in comparison to twins at low risk.

In this study, awakening and evening salivary cortisol level of healthy adult MZ and DZ twins with (High-Risk twins) and without (Low-Risk twins) a co-twin history of affective disorder were measured, to test the hypothesis that a high genetic liability to affective disorder is associated with higher cortisol levels.

2. Methods

2.1. The registers

The Danish Civil Registration System assigns a unique personal identification number for all residents of Denmark. This number is linked to information on name, address, and date of birth. Information on death, emigration and immigration is also recorded in the system. All other Danish registers use the same unique identifier, and thus residents of Denmark can be tracked in all the public registers through record linkage. *The Danish Psychiatric Central Research Register* is nationwide, with registration of all psychiatric admissions and outpatient hospital contacts in Denmark for the country's 5.3 million inhabitants (Munk-Jorgensen and Mortensen, 1997). From April 1969 to December 1993, diseases were classified according to the International Classification of Diseases, 8th edition (ICD-8) (World Health Organization, 1967), and from January 1994, according to the International Classification of Diseases, 10th edition (ICD-10) (World Health Organization, 2005). *The Danish Twin Registry* was initiated in 1953 and contains information on 75,000 twin pairs born from 1870 to 2003. The completeness varies with the date of birth and is approximately 70% for the period before and close to 100% for the period after the Civil Registration System was established in 1968 (Kyvik et al., 1996; Harvald et al., 2004).

2.2. The linkage

Through record linkage between the Danish Twin Register, the Danish Psychiatric Research Register and the Danish Civil Registration System, a cohort of "High-Risk" twins was identified. This linkage identified same-sex twin