Psychoneuroendocrinology 66 (2016) 91–100

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Evidence of a unique and common genetic etiology between the CAR and the remaining part of the diurnal cycle: A study of 14 year-old twins

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ARTICLE INFO

Article history:
Received 22 September 2015
Received in revised form
10 December 2015
Accepted 17 December 2015

Keywords:
HPA axis
Cortisol
Diurnal rhythm
Genes
Twin studies
Cortisol awakening response

ABSTRACT

Introduction: By and large, studies have reported moderate contributions of genetic factors to cortisol secreted in the early morning and even smaller estimates later in the day. In contrast, the cortisol awakening response (CAR) has shown much stronger heritability estimates, which prompted the hypothesis that the etiology of cortisol secretion may vary according to the time of day. A direct test of this possibility has, however, not yet been performed.
Objective: To describe the specific and common etiology of the CAR, awakening level and cortisol change from morning to evening in an age-homogenous sample of twin adolescents.
Methods: A total of 592 participants of the Québec Newborn Twin Study, a population-based 1995–1998 cohort of families with twins in Canada, have collected saliva at awakening, 30 min later, at the end of afternoon and in the evening over four collection days.
Results: Multivariate Cholesky models showed both specific and common sources of variance between the CAR, awakening and cortisol diurnal change. The CAR had the strongest heritability estimates, which, for the most part, did not overlap with the other indicators. Conversely, similar magnitudes of genetic and environmental contributions were detected at awakening and for diurnal change, which partially overlapped.
Conclusion: Our study unraveled differences between the latent etiologies of the CAR and the rest of the diurnal cycle, which may contribute to identify regulatory genes and environments and detangle how these indicators each relate to physical and mental health.

1. Introduction

Cortisol, a glucocorticoid hormone secreted by the hypothalamus–pituitary–adrenal (HPA) axis, is involved in the regulation of many systems critical for well-being. Several cognitive and emotional functions also depend on it, such as attention, memory and regulating behavioral activation and inhibition. Cortisol typically follows a time-dependent pattern of secretion over the day, with higher levels normally present shortly after awakening followed by a rapid and then progressive decrease until a minimum is reached around midnight. This circadian rhythm emerges as a result of several ACTH driven pulses of cortisol, which are themselves under the control of several sources of influence coordinated by the central nervous system (Vis et al., 2012). Diurnal cortisol secretion receives a great deal of attention because of its proposed impact on a wide range of physical, psychological and behavioral difficulties (Fries et al., 2005; Susman, 2006). Central to this hypothesis is the great disparity in basal

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http://dx.doi.org/10.1016/j.psyneuen.2015.12.022
0306-4530/

secretion between individuals of all ages, including in the pattern of *change* of cortisol during the day (Smyth et al., 1997).

Many factors have been proposed to affect the circadian rhythm. These factors could, ultimately, be grouped into those present at the individual level and those emerging from the environment. Diurnal cortisol secretion has been associated with personal traits, such as optimism (Jobin et al., 2014) and fearfulness (Gunnar et al., 2009). Diurnal secretion has also been linked to early adverse experiences, such as maltreatment and neglect (Cicchetti et al., 2010; Fries et al., 2008; Tarullo and Gunnar, 2006). Similar findings are also emerging in regards to peer victimization in adolescence (Ouellet-Morin et al., 2011a,b; Vaillancourt et al., 2008), reflecting the sensitive nature of HPA axis activity to changing social environments. It remains unclear, however, to which extent these associations reflect acquired and/or inherited influences, as some experiences may partly arise as a function of the individuals' genetic makeup (Jaffee and Price, 2007). Delineating the etiology of cortisol circadian rhythm represents a key building block to ascertain its impact on health.

Most twin and parent-offspring studies conducted thus far have shown that cortisol secreted in the early hours of the morning is moderately inherited whereas lower estimates are detected later on (Bartels et al., 2003a; Franz et al., 2010; Kupper et al., 2005; Wüst et al., 2000). For example, Kupper et al. (2005) have reported moderate heritability estimates (33 and 34%) at awakening and 30 min later in adulthood, whereas non-significant genetic contributions were detected subsequently (Kupper et al., 2005). A similar pattern was found at an earlier age (Bartels et al., 2003a; Ouellet-Morin et al., 2009; Schreiber et al., 2006). Gustafsson et al. (2011) have shown moderate-to-high heritability estimates at awakening (28%) and in the cortisol response to awakening (CAR; 60%), but a low genetic contribution in the evening (8%). Based on these findings, it is proposed that cortisol secreted at awakening and thereafter may have a distinct etiology. Such possibility may arise if distinct genetic and environmental factors are involved (i.e., qualitative differences) and/or because the magnitude of these contributions differs as the day goes by (i.e., quantitative differences) (Bartels et al., 2003a; Edwards et al., 2001; Gustafsson et al., 2011; Kupper et al., 2005; Schmidt-Reinwald et al., 1999; Wilhelm et al., 2007; Wüst et al. 2000). A direct test of this possibility requires performing multivariate genetic models estimating simultaneously the genetic and environmental contributions. To the best of our knowledge, no study has yet performed this test.

Our understanding of the etiology of diurnal cortisol secretion may also be limited by the fact that few studies have been conducted in youth. This is surprising on many accounts. First, basal cortisol secretion undergoes important changes during the first two decades of life, with decreasing levels noted from toddlerhood to mid-childhood followed by an opposite trend (Adam, 2006; Gunnar et al., 2009; Shirtcliff et al., 2011). These maturational changes may depend on changing social environments (e.g., daycare to formal schooling), neuroendocrine factors (e.g., sex hormones) and brain structures and functioning (e.g., prefrontal cortex; (Gunnar and Vazquez, 2006; Lupien et al., 2009). Second, the dearth of studies describing the genetic and environmental etiology of diurnal cortisol secretion in adolescence is at odds with the documented increase of mental health problems during this time. Third, the genetic and environmental estimates derived from the adult samples may not be generalized to younger samples, because older twin pairs may face greater disparity in their daily routines. The use of age-heterogeneous samples to describe the genetic and environmental etiology of cortisol secretion may help increase the precision of these estimates.

Obtaining precise etiology estimates of the cortisol circadian rhythm also depends on our capacity to summarize all the available information according to indicators that depart from single point analyses. Statistical approaches such as linear growth curve models (LGCM) are increasingly used, because they simultaneously estimate the morning cortisol level and the changes occurring thereafter. In addition to maximizing statistical power, they easily accommodate unequal observations across individuals (missing data) and control for time-varying covariates (e.g., time of collection). Combined with confirmatory factorial analyses, LGCM contribute to tease apart "trait-like" from "situation-specific" variation.

The present study aims to describe the genetic and environmental etiology of diurnal cortisol secretion in mid-adolescence. More specifically, we tested whether it is possible to derive stable patterns of diurnal cortisol secretion from samples collected across multiple days. We then estimated the genetic and environmental contributions of individual differences in the CAR and cortisol change from morning to evening and examined whether these factors are shared or are rather specific to each indicator.

2. Methods

2.1. Sample

Participants were part of the Québec Newborn Twin Study, a sample of twins recruited between 1995 and 1998 in the greater Montreal area. A total of 989 families with twins were contacted after the twins' birth, of which 672 agreed to participate (68.0%). Twins were first seen when they were 5 months of age and then prospectively assessed for a variety of child and family characteristics. The present study focuses on data collected when the twins were 14 years-old [mean (standard deviation or SD), 14.00 (.28)]. Valid data was available for 592 twins [280 monozygotic (MZ), 204 same-sex dizygotic (DZ) and 108 mixed-sex DZ twins] from whom most (74%) had collected saliva at each of four collection days. The families were comparable to another sample of single births in the province of Québec. At the time of their children's birth, 95% of parents lived together, 44% of the twins were the firstborn children, 66% of mothers and 60% of fathers were between 25 and 34 years old, 17% of mothers and 14% of fathers had not finished high school, 28% of mothers and 27% of fathers held a university degree, 83% of the parents were employed, 10% of the families received social welfare or unemployment insurance, and 30% of families had an annual income of <$30,000. Most families were of European descent (87%), 3% were of African descent, 3% were of Asian descent, and 1% were Native North Americans. Zygosity was assessed by using 8–10 highly polymorphous genetic markers. Twins were diagnosed as MZ when concordant for every genetic marker. When genetic material was insufficient or unavailable due to parental refusal (43% of cases), zygosity was determined based on physical resemblance questionnaires at 18 months and again at age 9 (Spitz et al., 1996). The comparison of both methods in a subsample of 237 same-sex pairs revealed a 94% correspondence rate.

2.2. Procedure

Letters explaining the objectives of the study were sent to the families, followed by a home visit. After informed consent from the parents and assent from the participants were obtained, the research assistants explained the collection protocol, which consisted in sampling saliva at four time points during the day (at awakening, 30 min later, late in the afternoon and bedtime) on four collection days (Tuesdays and Thursdays on two consecutive weeks). The research assistants made sure that the participants (and their parents) were familiar with the material. The families were visited a second time to gather the saliva tubes. All