Original article

Diurnal Cortisol Interacts With Stressful Events to Prospectively Predict Depressive Symptoms in Adolescent Girls

Keke L. Schuler, M.S. [a,*], Camilo J. Ruggero, Ph.D. [a], Brandon L. Goldstein, M.S. [b], Greg Perlman, Ph.D. [c], Daniel N. Klein, Ph.D. [b], and Roman Kotov, Ph.D. [c]

[a] Department of Psychology, University of North Texas, Denton, Texas
[b] Department of Psychology, Stony Brook University, Stony Brook, New York
[c] Department of Psychiatry, Stony Brook University, Stony Brook, New York

A B S T R A C T

Purpose: The aim of present study was to test the diathesis-stress model of depression using baseline cortisol, prospective assessment of depression symptoms, and stressful life events.
Methods: The sample consisted of 527 adolescent girls aged 13.5–15.5 years without major depressive disorder. At baseline, saliva samples were collected at waking, 30 minutes after waking, and 8 P.M. on 3 consecutive days. Diurnal cortisol was indexed by cortisol awakening response (CAR) and area under the curve with respect to ground (AUCg). Stressful events during the preceding interval and current depressive symptoms were assessed 18 months following baseline.
Results: Stressful events and the interaction of CAR or AUCg with stressful events predicted depressive symptoms at 18 months, even after controlling for baseline depressive symptoms. Specifically, in the face of high levels of stress, baseline blunted CAR or smaller AUCg were associated with future depressive symptoms. This was more apparent for CAR than AUCg. The effect was reversed at low levels of stress, with heightened CAR associated with more severe depressive symptoms.
Conclusions: Blunted CAR and less daily cortisol output at baseline appear to accentuate the depressogenic effects of stressful events after 18 months, consistent with the diathesis-stress model of hypothalamic-pituitary-adrenal axis function in depression.

IMPLICATIONS AND CONTRIBUTION

Findings from the present study imply that blunted cortisol awakening response and less daily cortisol output are associated with the development of depressive symptoms after experiencing stressful events in adolescent girls. Findings contribute to current understanding of biological risk factors for major depressive disorder in early adolescence.

Major depressive disorder (MDD) is a serious mental health problem in adolescent girls, who face prevalence rates more than double that of boys (10.7% vs. 4.6%, respectively) [1], making it imperative to identify factors that put them at risk. Stress is a well-documented risk factor for depressive disorders and symptoms, including among adolescent girls [2–6]. Numerous studies have documented the onset of MDD or depressive symptoms during adolescence following life stress [2–6]. However, other studies reported no such effect [7]. Hence, stress by itself may be necessary but not sufficient for youth to develop MDD or depressive symptoms [8]. Rather, certain youth may be at increased risk of developing the disorder in the face of stress [8]. Indeed, the diathesis-stress model of depression posits that the influences of stress on depression partly depend on individuals' sensitive to the deleterious effect of stress [9].

A number of biological factors have been investigated as potential markers of stress sensitivity (i.e., diatheses), and some of them have been linked to MDD. One such factor is altered hypothalamic-pituitary-adrenal (HPA) axis, which is reflected in

dysregulated diurnal cortisol. The HPA axis is a neuroendocrine system and one of the most fundamental physiological systems involved in responding to stress [10]. Importantly, the HPA axis is responsible for mobilizing energy resources within the body and maintaining individuals' homeostasis during the stress response [10].

In an early attempt to test the diathesis-stress model of depression in adolescents, researchers examined whether dysregulated diurnal cortisol alone could be a potential diathesis associated with MDD, even without regard to stress. Evidence from prospective studies has shown that several indices of diurnal cortisol were associated with MDD onset and symptom acceleration in adolescents. For example, increased levels of morning cortisol alone were reported to predict MDD onset [11–13]. Recent studies have reported that one index of diurnal cortisol in particular, the cortisol awakening response (CAR), was a significant prospective predictor of the onset of MDD across a 2.5-year follow-up period in older adolescents [14,15]. Specifically, every standard deviation increase in CAR doubled the risk for MDD [15]. However, contradictory findings were also reported in two studies, indicating CAR did not prospectively predict MDD onset in youth [8,16].

A second index of diurnal cortisol, cortisol area under the curve with respect to ground (AUCg), has received increasing attention in research for three reasons [8,17]. First, distinct from CAR, AUCg represents total volume of daily cortisol output [17,18]. The formula used to calculate AUCg incorporates multiple time points, daily cortisol fluctuation, and total volume of cortisol circulation [8,18]. As such, AUCg may provide a more comprehensive picture regarding basal activity of the HPA axis. Second, among the diurnal cortisol indicators studied in the literature (e.g., CAR, diurnal slope, and AUCg), AUCg is evidenced to be the most stable index, demonstrating the least day-to-day variability (followed by diurnal slope and CAR) [19–21]. The stability of AUCg makes it a good candidate to represent individuals' trait-like characteristics. Third, AUCg has been associated with the development of MDD. Evidence from a prospective study suggested that higher levels of daily cortisol tripled risk for a major affective disorder in adolescents [22]. However, Vrshek-Schallhorn et al. [15] reported no such effect of AUCg, indicating AUCg alone did not predict MDD onset.

Direct tests of the diathesis-stress model of depression require assessments of depression, diurnal cortisol, and stressful events in a prospective design. Such studies of adolescents are rare. So far, two studies using naturalistic stressful events have reported mixed findings [8,15]. In both studies, results showed no interaction effect between CAR and stressful events on MDD onset [8,15]. Only one study revealed high levels of AUCg interacted with naturally occurring stressful events to predict MDD onset in adolescent girls with no history of psychopathology [8], whereas the other study did not report the interaction between AUCg and stressful events [15]. Thus, support for the diathesis-stress model of depression in adolescence is mixed, possibly due to inconsistency in measuring cortisol (e.g., in the context of stress [8,15] vs. alone without regard to stress [11–13]) or stressful events (e.g., chronic stress over a year [15] vs. self-reported stress over a few years [8]).

The aim of the present study was to directly test the diathesis-stress model of depression using a larger sample of adolescent girls with no history of psychopathology and an objective assessment of stressful events. We assessed whether the interaction between baseline diurnal cortisol and intervening stressful events would prospectively predict self-reported depressive symptoms 18 months later.

Methods

Participants

Adolescent girls (N = 550) aged 13.5–15.5 years (M_{age} = 14.39, standard deviation = .62) and one of their biological parents were recruited for the Adolescent Development of Emotions and Personality Traits project. Participants were mostly recruited using phone lists, and all families were financially compensated for their participation [23]. Inclusion criteria of the Adolescent Development of Emotions and Personality Traits project were ability to read and understand English questionnaires and participation of at least one biological parent [23]. To ensure a healthy adolescent sample, exclusion criteria included lifetime history of MDD, dysthymia, or intellectual disabilities, habitual smoking, and medication use (i.e., anti-inflammatory drugs) or disease that might potentially influence the activity of the HPA axis [23]. The absence of a lifetime history of MDD or dysthymia at the baseline assessment was confirmed by a diagnostic interview using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (KSADS) [24]. Diagnostic interviews were conducted by experienced interviewers under supervision of clinical psychologists (R.K., G.P., and D.K.) [23]. No adolescent in the sample was diagnosed with MDD based on KSADS. In total, 23 adolescent participants were deemed as outliers (see Statistical analyses for details of outlier analysis), leaving a final sample of 527 adolescents. Racial and ethnic composition of the final sample was 81.6% non-Hispanic white. The study was approved by the Stony Brook University Institutional Review Board. Informed parental consent and adolescent assent were obtained.

Clinical assessments

Inventory of Depression and Anxiety Symptoms (IDAS-II) [25] General Depression scale was used to assess adolescents' depressive symptoms at baseline and 18 months. The IDAS-II is a 99-item self-report measure with 18 specific scales plus General Depression. Each symptom in the scale was rated on a five-point Likert scale from 1 (not at all) to 5 (extremely) [25]. The scale had excellent internal consistency at baseline and 18 months (α's = .89 and .91, respectively).

The Stressful Life Events Schedule [26] was used to assess for intervening stressful events (e.g., death of family or friends) at 9 months and 18 months. The Stressful Life Events Schedule is an interview instrument, which was designed to examine the relationship between stress and depression in children and adolescents [26]. At each follow-up assessment, adolescents were interviewed about their stressful events that had happened during the preceding interval. Consistent with administration guidelines, events were rated by consensus of trained interviewers on a four-point scale (1, 2, 3, and 4; "objective threat ratings") [26]. A total score of stressful events was calculated by squaring objective threat rating for each event and summing the squared ratings [26].

Biological assessments

Saliva samples collection and cortisol assay. Adolescent participants collected saliva samples three times a day (upon waking,