Review Paper

The Cortisol Awakening Response in Bipolar Illness: A Pilot Study

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Objective: A growing body of data suggests that a significantly enhanced salivary cortisol response to waking may indicate an enduring tendency to abnormal cortisol regulation. Our objective was to apply the response test to a population already known to have long-term hypothalamo–pituitary–adrenocortical (HPA) axis dysregulation. We hypothesized that the free cortisol response to waking, believed to be genetically influenced, would be elevated in a significant percentage of cases, regardless of the afternoon Dexamethasone Suppression Test (DST) value.

Method: Using the free cortisol response to waking and the short daytime profile, we tested 18 clinically stable, lithium-responsive subjects from our long-term naturalistic follow-up of monthly DSTs. These tests include salivary testing every 15 minutes during the first hour of waking, followed by samples taken at 3:00 PM and 8:00 PM.

Results: While clinically stable on lithium prophylaxis, patients with bipolar disorder (BD) showed a significantly enhanced salivary cortisol response to waking, compared with control subjects ($P < 0.03$). Cortisol levels 30 minutes after waking significantly exceeded those in the large normative data provided in the literature ($P < 0.001$).

Conclusions: Our observations support the hypothesis that the free cortisol response to waking can reflect relatively enduring HPA dysregulation, even when lithium-responsive BD patients are clinically well and their DSTs are normal. Because the test is easy to administer, the free cortisol response to waking may hold promise as a marker in studies of high-risk families predisposed to, or at risk for, mood disorders.

(Can J Psychiatry 2003;48:462–466)

Information on funding and support and author affiliations appears at the end of the article.

Clinical Implications

- A growing body of literature points to hypothalamo–pituitary–adrenocortical (HPA) axis dysregulation as a critical factor in the development of mood disorders.
- Long-term enhanced cortisol secretion may have important health ramifications in addition to its contribution to mood syndromes.
- The free cortisol response to waking is a promising series of salivary tests that may provide a useful and noninvasive measure of HPA functioning in high-risk studies.

Limitations

- The small sample size limits generalizability of our findings.
- Because interrupted sleep may interfere with the waking cortisol rise, we may have underestimated the proportion of our population with enhanced cortisol secretion.
- Highly cooperative participants are required.

Key Words: *glucocorticoids, salivary cortisol, bipolar disorder, lithium, Dexamethasone Suppression Test, DST*

The Relation Between Cortisol and Mood Disorders

For several decades, strong associations have been made between hypothalamo–pituitary–adrenocortical (HPA) axis dysregulation and mood disorders (1,2). During the 1980s, investigators focused on cross-sectional associations between cortisol and melancholic depression, using the Dexamethasone Suppression Test (DST). It has been reported that approximately 70% of patients meeting criteria for melancholic depression do not show suppressed cortisol secretion after dexamethasone challenge (3). Further studies using the DST have shown that some individuals suffering from mood disorders have positive DSTs even after their clinical depression has improved and that these periods of cortisol nonsuppression correlate with heightened risk of relapse (4). Intermittent nonsuppression has also been used to predict high-risk periods for episode recurrence (5,6).

Recently, interest has turned to more refined testing and the probability that HPA dysregulation may even predate the onset of clinical illness (7). Preliminary data suggest that this dysregulation may be concentrated within the families of individuals with mood disorders (7), suggesting the hypothesis that early abnormalities in cortisol regulation may confer a risk for the future development of mood disorders.

To understand the temporal relation between HPA dysregulation and the onset of bipolar disorder (BD), it is essential to have a reliable and noninvasive test that can be repeatedly administered prospectively and is acceptable to high-risk populations. Promising candidates for such a test include the salivary free cortisol response to waking and the short daytime profile, a test that adds afternoon and evening measurements to the waking values.

This pilot study builds on a long-term naturalistic study of patients with a highly recurrent typical BD stabilized with lithium monotherapy. Using monthly DSTs for more than 6 years, we have already established extended patterns of enhanced cortisol secretion in this group. The goal of this pilot investigation was to apply the salivary cortisol testing to the same group.

The Free Cortisol Response to Waking and the Short Daytime Profile

Salivary cortisol levels are about 5% of the concentrations present in the serum (8,9), representing the unbound fraction. They correlate reliably with serum and cerebrospinal fluid (CSF) levels, lagging the pulsatile pattern of adrenal secretion by approximately 15 minutes (10,11).

The cortisol response to waking is a rapid increase in salivary cortisol levels—at least 2.5 nmol/L above the individual morning baseline. It is normally observed within the first 30 minutes of waking (12). According to preliminary data, enhanced secretion is seen in people reporting chronic anxiety, social stress, and perceived lack of social recognition (12). Wust and others have reported a mean rise of 50% in 509 German control subjects (12).

The cortisol rise is consistent, and a moderate rise is present in 75% of the general population. While women show a virtually identical cortisol rise after awakening, compared with men, they tend to have a significantly delayed decrease (12). The free cortisol response to waking test comprises 4 saliva samples taken at 15-minute intervals, immediately upon waking.The test shows a high degree of intraindividual stability and has been shown to be under substantial genetic influence (12–14).

The short daytime profile comprises 3 salivary tests. The first is taken within 1 hour of waking, and the next 2 are taken at 3:00 PM and 8:00 PM, respectively. Recent observations in large samples suggest that approximately 85% of the general population show a declining pattern from morning to night. However, 15% tend to show a relatively flat short daytime profile, defined as an AM-to-PM decline of less than 5% (14). Investigations into the health implications of a flattened response curve are being actively pursued, and initial data point to a poorer outcome in breast cancer patients showing this pattern, compared with those having a typical AM-to-PM decline in cortisol (15). In contrast to the more stable cortisol response to waking, the short daytime profile has shown a lack of similarity between twin siblings and is believed to be more sensitive to immediate circumstances (16).

Methods

Study Population

At the Royal Ottawa Hospital, 18 patients with frequently recurrent BD were enrolled into the study (9 men and 9 women; mean age 52 years, SD 12). According to an assessment based on the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L) and all available information, the subjects met DSM-IV criteria for BD I (17). All showed full clinical remission on lithium monotherapy and were monitored with monthly DSTs for up to 13 years. No participants had concurrent medical conditions or active substance abuse nor were they receiving steroid replacement. The patients studied in this project were previously involved in an ongoing naturalistic follow-up of lithium-responsive BD. In work already published, we describe long-term patterns of DST positivity in this cohort (18). In addition to the BD patients, we tested 5 healthy control subjects (aged 13 to 66 years) with no personal or family history of major affective disorders. For statistical comparison, we also used the data from 509 healthy control subjects, as described by Wust (12).

Protocol

Salivary Samples. Individuals were asked to submit salivary samples during 1 weekend day preceding their regularly scheduled DST. All participants were judged by direct interview to be in full clinical remission. All subjects were given a set of labelled salivettes and detailed instructions, both written and verbal. Collection times were as follows: at waking; 15, 30, and 45 minutes after waking; at 3:00 PM; and at 8:00 PM. Subjects were asked not to brush their teeth before completing

Table 1 Summary of salivary results

Patient	Morning Rise %	AM/PM ratio %	Latest DST	Positive DST %
1	72.0	–75.4	Positive	68.0
2	547.2	25.0	Positive	66.0
3[a]	–37.0	–80.0	Negative	6.0
4	89.6	–91.0	Negative	10.0
5	103.0	–87.5	Negative	46.0
6	10.5	–91.0	Positive	49.0
7	68.7	–87.5	Positive	50.0
8	31.8	–72.7	Negative	13.0
9	–0.527	–87.5	Negative	37.0
10	124.0	–81.5	Negative	3.5
11	65.7	–76.3	Negative	13.0
12	48.0	–94.3	Negative	48.0
13	–57.0	–87.7	Negative	31.0
14	231.0	–91.0	Negative	1.0
15[a]	–0.168	–83.5	Negative	14.0
16	32.8	–80.3	Negative	0.0
17	108.0	–87.1	Negative	4.3
18	93.0	–94.2	Negative	72.0

This table shows percentage morning rise from baseline, AM/PM ratio (%), latest dexamethasone supression test (DST) result, and the percent positive DSTs on record from serial monthly testing.

[a]Denotes a patient report of poor sleep the night before salivary profiling.

the morning saliva sampling, to avoid food intake before saliva sampling, to avoid vigorous exercise on the test day, and to record the duration of their sleep the night before testing. After collecting the salivettes, study participants froze them in their home freezers prior to pick-up by a member of our team. The salivary cortisol assay was the DSL-2000 cortisol RIA (Diagnostic Systems Laboratories Inc, Webster, Texas), modified for saliva. Because of high interlaboratory variability in salivary cortisol, analysis was done at Dr Michael Meaney's laboratory (McGill University, Montreal, Quebec), a laboratory with extensive experience in cortisol analysis.

Dexamethasone Suppression Tests. Participants took 1 mg dexamethasone at 11:00 PM the night before the test, which was conducted the day following the salivary profile. A blood sample for serum cortisol was drawn at 4:00 PM the next day. Cortisol levels over 138.5 nmol/L were considered positive (3).

The Research and Ethics Committee of the Royal Ottawa Hospital, Ottawa, Canada, approved these procedures.

Statistical Analysis

We compared the salivary cortisol data from patients with a small sample of Canadian control subjects and a large population of German control subjects. To compare the quantitative data from our patients with the Canadian control subjects, we used Mann–Whitney *U* tests and Kolmogorov–Smirnov 2-sample tests. We used the *t*-test for comparison with German control subjects.

Results

There was a significant difference between BD patients and our control subjects in the maximum percentage rise of salivary cortisol response to awakening (patient mean 96.11, standard error of the mean [SEM] 32.01; control subject mean 10.60, SEM 10.60; Mann–Whitney $U = 16.00$, $P < 0.03$; Table 1). Those showing a waking response also had significantly higher mean cortisol values at 30 minutes after waking, compared with 509 normal subjects described in Wust and others' study (12) (patient mean 27.1 nmol/L, SD 9.67; control subject mean 22.95 nmol/L, SD 9.13; 1-tail *t*-test $P < 0.001$) Baseline values at time zero, immediately upon waking, did not differ significantly between our sample and Wust's control subjects (12) (patient mean 15.98 nmol/L, SD 7.99; control subject mean 15.12 nmol/L, SD 6.25).

Patients and our 5 control subjects did not differ significantly in the percentage decline from the peak morning value to the evening values ("AM/PM ratio"; patient mean 79.09, SEM 6.30; control subject mean 83.75, SEM 9.95).

The mean number of DSTs available per patient was 64.9 (SD 36). The patients included in the DST study had between 3.5% and 84.3% positive (DST mean 25.75, SEM 5.00, median 13.5); the values did not correlate significantly either with AM/PM drop ($r = 0.132$, ns) or with maximum morning rise of salivary cortisol ($r = 0.103$, ns).

Figures 1, 2, and 3 illustrate a representative example—a woman (Patient 1) we have treated for recurrent bipolar illness for 25 years and whose intermittently positive DSTs we have monitored (Figure 1). Her most recent DST was negative, her AM-to-PM decline was normal (state measures), and she continued to be in full remission (Figure 3). Yet, her morning rise of salivary cortisol (trait-like) was higher than average at 72% (Figure 2), presumably expressing her BD propensity.

Discussion

In this pilot investigation, euthymic lithium-responsive BD I patients showed significant enhancement of the salivary morning cortisol response to waking, compared with a small group of Canadian healthy control subjects and a large group of German healthy control subjects. The patients had a history of recurrent BD, but when tested, they were experiencing full remission on several years' treatment with lithium, and their most recent DSTs tended to be normally suppressed. This observation suggests that an excessive cortisol rise in response to waking may be a relatively enduring marker characteristic of bipolar illness, independent of momentary state as reflected by the DST. Conversely, nonsuppressed elevated cortisol in the DST test is considered a useful state marker for many patients with acute depression and mania, as has been established in many studies.

Our observations are consistent with a view that both the DST and the short daytime cortisol profile reflect relatively transient aspects of cortisol regulation, since these tests tended to be normal even when the waking response was abnormal.

The morning cortisol response was not correlated with either the short daytime profile or the percentage of positive DSTs on record. This suggests that, indeed, the morning cortisol rise

Figure 1 Longitudinal Dexamethasone Suppression Test (DST) data on a fully remitted lithium responder for past 5 years who was asymptomatic and treated with lithium throughout

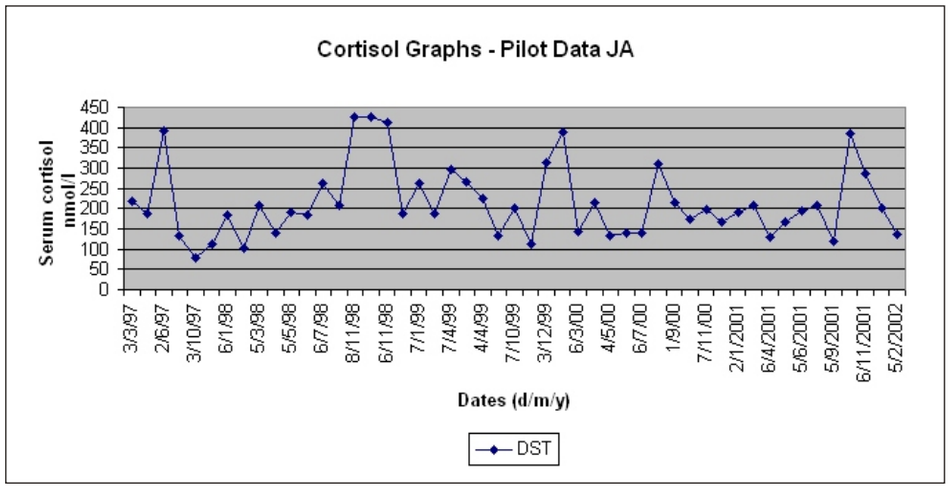


Figure 2 Robust free cortisol response to waking

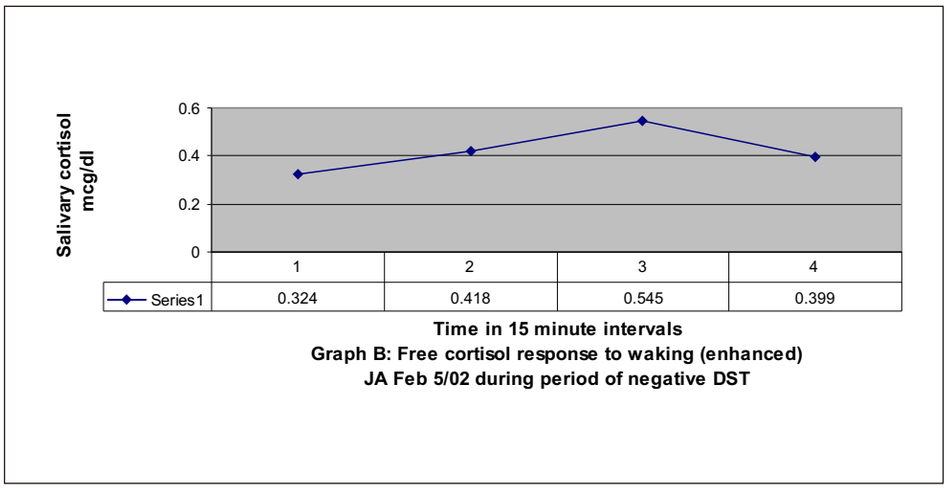
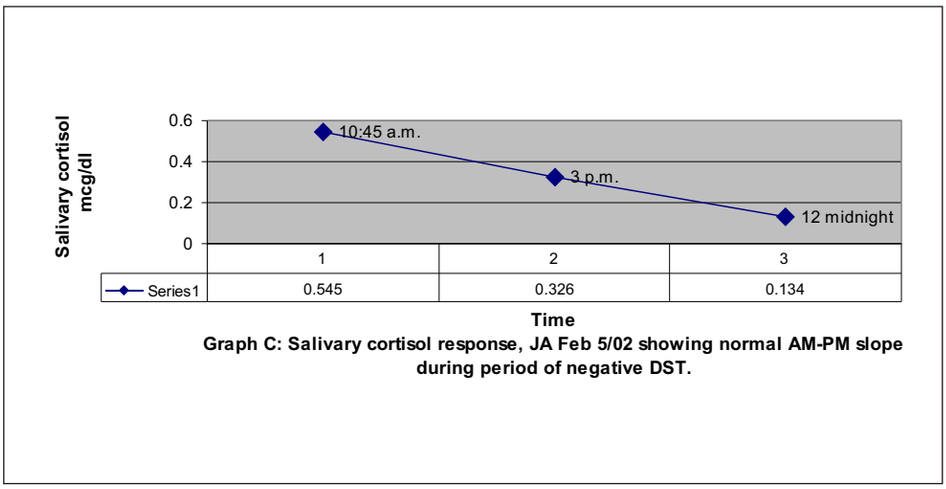


Figure 3 Salivary cortisol response



and the behaviour of cortisol during the day and late afternoon reflect 2 different properties of the HPA axis. The greater-than-expected morning rise of salivary cortisol was present in most tested patients, but not in all. Adjusted methodology could lead to even more patients with a dramatic morning rise. For instance, it will be important in further testings to ensure that the tested patients have slept normally during the night preceding the test and that the first sample is taken immediately after awakening.

Hellhammer and others have observed this problem, and somnographic studies are underway to elucidate the relation between the free cortisol response and sleep problems (Hellhammer, personal communication, 2002). If the rise occurred at a time other than during our specified collection interval, we have underestimated the proportion of our sample exhibiting the abnormal test. Conversely, it must be kept in mind that 23% of the normal population does not show the waking response at all (12). Individuals with BD not demonstrating a rapid waking response may be a part of that cluster.

If the free cortisol response to waking identifies a vulnerability factor for the illness in such high-risk contexts as family studies (7), it will be essential to determine the retest stability in this population. The initial study design did not take this into account, and future studies will have to address the stability of both normal and abnormal results in BD patients. While restricted by a small sample and limited control subjects, the findings of this pilot study support further investigations into the relation between the free cortisol response to waking and BD.

Funding and Support

This study was supported by the University of Ottawa University Medical Research Fund (UMRF).

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Manuscript received May 2003, revised, and accepted June 2003.
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Résumé : La réaction de cortisol au réveil dans la maladie bipolaire : une étude pilote

Objectif : Un ensemble de données croissantes suggèrent qu'une réaction de cortisol salivaire significativement accrue au réveil peut indiquer une tendance durable à une régulation anormale du cortisol. Notre objectif consistait à appliquer le test de réaction à une population déjà réputée avoir un dérèglement à long terme de l'axe hypothalamo–hypophyso–surrénalien (HHS). Nous avons émis l'hypothèse que la réaction libre de cortisol au réveil, que l'on croit d'influence génétique, serait élevée chez un pourcentage significatif de cas, peu importe la valeur l'après-midi de l'épreuve de freinage à la dexaméthasone (EFD).

Méthode : Nous avons testé 18 sujets cliniquement stables et réagissant bien au lithium de notre suivi naturaliste à long terme d'EFD mensuelles, à l'aide de la réaction libre de cortisol au réveil et du profil de jour court. Ces tests comprenaient une analyse de salive toutes les 15 minutes durant la première heure du réveil, suivie d'échantillons prélevés à 15 h et à 20 h.

Résultats : Bien que cliniquement stables grâce à un traitement au lithium, les patients souffrant de trouble bipolaire (TB) ont montré une réaction salivaire de cortisol significativement accrue au réveil, comparativement aux sujets témoins ($P < 0{,}03$). Les niveaux de cortisol, 30 minutes après le réveil, excédaient significativement la vaste quantité de données normatives fournies par la documentation ($P < 0{,}001$).

Conclusions : Nos observations soutiennent l'hypothèse selon laquelle la réaction libre de cortisol au réveil reflète un dérèglement relativement durable de l'axe HHS, même lorsque les patients souffrant de TB et réagissant bien au lithium sont cliniquement bien et que leurs EFD sont normales. Parce que ce test est facile à administrer, la réaction matinale au réveil peut promettre de constituer un marqueur pour les études des familles à risque élevé de troubles de l'humeur, ou qui y sont prédisposées.