Asian Journal of Psychiatry 1 (2008) 33–36

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

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

Investigating associations between cortisol and cognitive reactivity to sad mood provocation and the prediction of relapse in remitted major depression

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ARTICLE INFO

Article history:
Received 1 August 2008
Accepted 24 September 2008

Keywords:
Cortisol
Mood induction
Relapse
Depression
Cognitive reactivity

ABSTRACT

Overview: In remitted depressed patients, an increase in dysfunctional thoughts following a sad mood induction can predict relapse over 18 months. The current analysis examined whether salivary cortisol levels could also predict relapse in these same individuals.
Method: 99 subjects with major depression were first treated to full remission using either antidepressant medication or cognitive behavioural therapy. While in the remitted state, subjects were exposed to sad music to trigger dysfunctional thoughts. In a subset of 55 subjects, salivary cortisol levels taken before and after the mood challenge were also obtained.
Results: Unexpectedly, cortisol levels tended to decrease rather than increase following the mood challenge, suggesting that anticipation of the mood challenge was more stressful than the challenge itself. We thus used pre-challenge cortisol levels as the main grouping variable. Based on Kaplan–Meier survival curves, among subjects with low pre-challenge cortisol levels, those with a history of three or more prior episodes had significantly higher rates of relapse than did subjects with two or less prior episodes. In subjects with high pre-challenge cortisol levels, there was no significant difference in rates of relapse based on the number of prior episodes.
Conclusion: In depressed patients with few prior episodes, assessing risk of relapse and thus establishing the duration for treatment can be a difficult clinical problem. Pending replication, the current results suggest that high anticipatory cortisol levels may have utility in predicting relapse even in patients with few prior episodes.

1. Introduction

While a large body of research has examined vulnerability factors associated with depression, the vast majority of these studies have been done in currently depressed subjects. It is now well-established that at least 50% of patients recovered from depression are at high risk for further relapse (Belsher and Costello, 1988; Coryell and Winokur, 1992). Despite this, there is a dearth of research examining vulnerability factors and predictors of relapse that might be present in the remitted state. Improving our understanding of factors that predispose individuals to relapse in depression may help decrease the chronicity and morbidity associated with this illness.

The hypothalamic-pituitary-adrenal (HPA) axis has been a major focus of work in this area. For example, numerous studies have examined whether non-suppression to the dexamethasone suppression test (DST) predicts future relapse in recovered depressed patients. A meta-analysis of the DST by Ribeiro et al. (1993) concluded that while DST results during a depressive episode do not have prognostic value, non-suppression of cortisol following successful treatment is strongly associated with a poor outcome. Subsequent studies in recovered inpatients and outpatients demonstrated that abnormalities on the combined dexamethasone/corticotropin-releasing hormone (DEX/CRH) test also predict recurrence of depression (Appelhof et al., 2006; Hatzinger et al., 2002; Zobel et al., 2001).

Another line of research has examined cognitive vulnerability in remitted patients as a predictor of relapse. For example, Segal et al. (2006) demonstrated that in recovered depressed patients,

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doi:10.1016/j.ajp.2008.09.006

cognitive reactivity in response to a mood challenge significantly predicted relapse over the subsequent 18 months. This suggests that both hormonal and cognitive measures are predictive of relapse in recovered depressed patients. However, empirical studies inclusive of both cortisol and cognitive measures in remitted depressed subjects have been scarce and inconsistent. In a cross-sectional study, Bos et al. (2005) reported that higher 24-h urinary cortisol measurement and increased fear perception were independently associated with recurrent depression in remitted depressed subjects. In contrast, Bouhuys et al. (2006) found an interaction between fear perception and cortisol in predicting relapse in remitted depressed subjects.

The current study aims to clarify associations between cognitive and cortisol vulnerability factors in remitted major depression. Prior work described above has examined baseline cortisol levels which reflect only one component of HPA axis activity. This study aims to build on prior work by examining both cortisol and cognitive reactivity to a sad mood challenge which may provide a more accurate means of assessing the sensitivity of these two systems. As cognitive reactivity has previously been shown to be associated with relapse in remitted depressed subjects (Segal et al., 2006), our main objective was to evaluate whether cortisol reactivity to the mood challenge also predicted relapse in this population. Following this we aimed to evaluate whether there is an association between cortisol and cognitive responses to the mood challenge in predicting relapse. Our hypothesis was that increased cortisol responses to sad mood provocation would also predict relapse in remitted depression. In addition, we hypothesized that there would be an association between cortisol and cognitive activation in predicting relapse.

2. Methods

The mood challenge was conducted as part of a larger study to examine cognitive predictors of depressive relapse (Segal et al., 2006). In brief, in Phase 1 of this study, 301 patients with Major Depressive Disorder (MDD) were randomized to receive either cognitive behavioural therapy (CBT) or antidepressant therapy. In Phase 2 of the study, subjects who remitted from depression underwent a mood provocation protocol and were followed for 18 months.

Fifty-five, out of a total of 99 outpatients with MDD who achieved remission and underwent mood challenge provided cortisol measures both before and after the sad mood provocation. Of these 55 subjects, 23 had received antidepressant therapy and 32 received CBT as part of Phase 1 of the study.

Cortisol was obtained from saliva using salivettes. Samples were obtained at times −25, 0, +25, +45 and +65 min relative to the mood induction protocol.

2.1. Mood provocation

Subjects were asked to listen to a music piece titled "Russia under the Mongolian Yoke", while being asked to recall a sad time in their lives. Previous studies (e.g. Clark and Teasdale, 1985) have shown that this type of protocol with elements of sad music and autobiographical recall can effectively induce a transient dysphoric mood (Martin, 1990).

2.2. Hormone assays

Saliva samples were obtained by having participants lightly chew on cotton-wool salivettes. Saliva samples were stored until analysis at a minimum of −20 °C. Cortisol concentrations were determined in saliva in duplicate by enzyme immunoassay (EIA) (Salimetrics; State College, PA, USA). The intra-assay variability was less than 10%.

3. Results

3.1. Demographics and clinical characteristics

A total of 55 (35 female) patients participated in the current sub-study with a mean age of 38.8 (10.1 S.D.). Mean Hamilton Depression Scale Score (Hamilton, 1960) was 4.6 (3.0 S.D.) and mean Beck Depression Inventory (Beck et al., 1996) score was 7.6 (5.6 S.D.), indicating that patients were euthymic post-treatment and at the time of the mood challenge. Regarding prior course of illness, 18 patients had 2 or less previous depressive episodes, whereas 37 patients had experienced 3 or more past depressions.

3.2. Do DAS change scores to mood induction predict relapse in this sub-sample?

Following Segal et al. (2006), we used residualized change in Dysfunctional Attitude Scale (DAS; Weissman, 1979) score as a continuous predictor in a Cox Proportional Hazards Regression to assess the relationship between cognitive reactivity and relapse in our sub-sample. The results indicated that the pattern of results in this subset of patients was the same as reported in the larger sample of 99 patients in Segal et al. (2006), i.e. we were able to replicate the finding that dysfunctional attitudes in response to the mood induction predicted relapse (Wald = 4.96, $p = .026$). In addition, as also reported in the larger study, subjects with three or more prior episodes were significantly more likely to relapse (23/37) vs. those with one or two prior depressive episodes (5/18; $\chi^2 = 5.7$, d.f. = 1, $p = .017$). This suggests that the sub-sample for the current study was representative of the larger sample of depressed patients in the overall study program.

3.3. Does cortisol reactivity to mood induction predict relapse?

As shown in Fig. 1, cortisol levels were highest at the initial time point (−25 min) and subsequently dropped over the course of the mood induction procedure. We thus concluded that the initial cortisol level was the best measure of cortisol reactivity in this study design, i.e. the time of maximum novelty and uncontrollability, factors previously associated with HPA activation to stress (Dickerson and Kemeny, 2004). For all subsequent analyses we used the −25 min cortisol sample (high or low based on a median split) as our main grouping variable. Log_{10} transformation of the

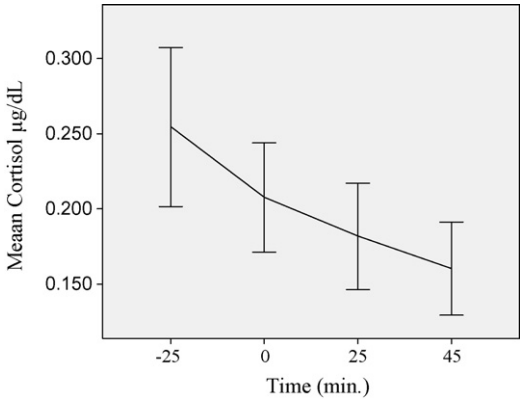

Fig. 1. Decline in cortisol levels during sad mood provocation in 55 patients remitted from major depression.