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Persistence of abnormal cortisol levels in elderly persons after recovery from major depression

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ABSTRACT

Background: Cortisol hypersecretion is characteristic of acute clinical depression, but little is known in fully recovered, non-treated elderly persons with a lifetime history of depression. This study was designed to examine patterns of diurnal cycle of cortisol in an elderly cohort without current depression or treatment for depression according to whether the person has or has not experienced a previous episode of depression or co-morbid depression with anxiety.

Methods: Cortisol secretion was evaluated in 162 community-dwelling elderly on a stressful and a non-stressful day (basal level). Past depression and anxiety disorders were assessed using a standardized psychiatric examination based on DSM-IV criteria (the Mini International Neuropsychiatric Interview).

Results: Antidepressant-free persons with a history of non-co-morbid major depression (6.8% of the sample) showed basal cortisol hypersecretion compared to those with depression and anxiety (8.6%) or controls. Several hours after exposure to a stressful situation, controls showed a sustained increase in cortisol secretion, which was not observed in persons with a history of depression. Persons with a history of depression with anxiety showed a similar cortisol secretion at baseline to controls but a heightened response to stressful situation; a pattern comparable to that observed in subjects with pure anxiety disorders (16.7%).

Conclusion: An abnormal HPA response persists even after effective treatment for depression. A history of co-morbid depression and anxiety gives rise to changes characteristic of anxiety alone. Our findings suggest that cortisol abnormalities may be trait markers for vulnerability to depression and for the differentiation of depression and depression with co-morbid anxiety.

1. Introduction

One of the more consistent physiological abnormalities reported in major depression (MD) is cortisol hypersecretion, although studies in community-based samples have been less conclusive (see for review Bhagwagar et al. (2008)). Cortisol hypersecretion was initially considered a state marker of MD, remitting with clinical improvement (see for reviews Holsboer (2000) and Young (2004)). More recently, however, persistent abnormalities have been noted in young non-depressed people at familial risk (Mannie et al., 2007) or in recovered depressed patients, particularly those at high risk of recurrence (Bhagwagar et al., 2003; Zobel et al., 2001), suggesting that such abnormalities could be markers of trait vulnerability to recurrent depression and may represent illness endophenotypes (Bhagwagar et al., 2008; Flint and Munafo, 2007; Hasler et al., 2004). This observation has not been investigated in the elderly, although hypothalamic-pituitary-adrenal (HPA) axis functioning may be especially vulnerable in this group given the accumulation of stressful events and high lifetime prevalence of MD (Ritchie et al., 2004). The study of elderly cohorts permits the examination of lifetime exposure to depression as well as patterns of recurrence.

Although some anxiety disorders also have been reported to be associated with neurobiological abnormalities, neither the lifetime persistence of cortisol abnormalities nor the impact of co-occurrence of depression with anxiety have been evaluated. Co-morbidity is common in the elderly (Lenze et al., 2000; Ritchie et al., 2004) and often indicative of more severe depressive symptoms, worse clinical course and higher risk of suicide (Brown et al., 1996; Clayton, 1990; Lenze et al., 2000). The few studies which have been conducted to date on anxiety co-morbidity and cortisol secretion

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have focused on small clinical samples of young adults with current MD and post-traumatic stress disorder (PTSD) or panic disorder, which are relatively uncommon in the elderly, in contrast with generalized anxiety disorder (GAD) or phobia (Ritchie et al., 2004). We recently reported an increased cortisol secretion in response to a naturalistic stressful situation in elderly people with GAD or phobia (Chaudieu et al., 2008). However, the neuroendocrine functioning in depression and the influence of co-morbidity in this elderly general population were not investigated.

The present study thus aims to evaluate if the diurnal cycle of salivary cortisol is modified in community-dwelling elderly persons who have recovered from a previous major depressive episode and whether co-morbidity with anxiety disorders could influence this pattern. Cortisol patterns were evaluated under two naturalistic but contrasting conditions, i.e., at home and following a stressful morning (hospital examinations).

2. Methods

2.1. Study population

The subjects (between 65 and 90 years) included in the analyses were part of the ESPRIT Project and selected by random sampling from the electoral rolls of the Montpellier district, in the South of France (Ritchie et al., 2004). The present analyses were conducted on a subsample of 201 subjects for whom salivary cortisol had been collected under both conditions, who were free of dementia and not being treated with medication likely to modify cortisol levels (glucocorticoids, hormonal replacement therapy and benzodiazepines) (Chaudieu et al., 2008). From this sample, 18 subjects (eight women and 10 men) reporting trauma exposure with distressing intrusions were further excluded, since we have previously reported that they have a modified pattern of basal cortisol level (Chaudieu et al., 2008). We also excluded subjects currently taking antidepressants (three women and five men) and two women with current MD, as well as 11 subjects with lifetime MD and co-morbid psychotic disorders or hypomania. This left 162 subjects in the present study. Written informed consent was obtained from all subjects, and the study was approved by the regional ethics committee.

2.2. Diagnostic instruments

A standardized psychiatric examination validated within the French general population (Lecrubier et al., 1997); the Mini International Neuropsychiatric Interview MINI (French version 5.00), was used to detect lifetime MD or anxiety disorders according to DSM-IV criteria (American Psychiatric Association, 1994). Cases detected by the MINI were reviewed by a panel of psychiatrists to validate the initial diagnosis. The MINI was also used to detect subjects reporting previous severe trauma and meeting criteria A and B for DSM-IV post-traumatic stress disorder (PTSD). Current depressive symptomatology was evaluated using the Center for Epidemiologic Studies-Depression (CESD) self-report questionnaire, the total score ranging from 0 to 60. A cut-off point of 23 or more has been demonstrated to differentiate major depressive disorder (Radloff and Locke, 1986). Current use of antidepressants was validated either by presentation of the prescription or the medication itself, and the type of medication was recorded according to the World Health Organisation's ATC classification (WHO, 2000).

2.3. Cortisol measurement

Subjects were instructed not to drink, eat or smoke for at least 30 min before saliva collection. As cortisol levels increase shortly after awakening (Van Cauter et al., 1996), subjects were asked to start the protocol at least 1 h after awakening (mean time 1.5 ± 0.8 h) and subsequently twice with a 6–7 h interval (the last sampling being collected before midnight) recording the exact time. Mean values for sampling time were 8.8 ± 0.3, 15.7 ± 0.7 and 21.7 ± 0.6 h. Cortisol levels were determined from saliva collection (Hellhammer et al., 1987) by direct radioimmunoassay (Diagnostic Systems Laboratories-Webster, Texas). Intra-assay and inter-assay coefficients of variation averaged 5%. For less than 5% of the samples, the values were lower than the detection limit, 10 ng/dl (0.27 nM) and were replaced by a value corresponding to the threshold value divided by two.

2.4. Baseline and environmental stress conditions (home and hospital visit)

As in other naturalistic studies, subjects were allowed to decide wake up and sleep times. Participants were encouraged to carry out their normal daily activities with limited physical exertion in order to maximize ecological validity. Samples were taken under two contrasting conditions; at the hospital ("stressful situation") where a lengthy clinical examination (between 08–11 h AM) was undertaken involving various recognized psychosocial stressors (e.g., psychiatric examination, cognitive testing, clinical evaluation and blood collection) and a subsequent quiet day at home (baseline condition). The first sampling at the hospital was performed just before the clinical examination.

2.5. Statistical analysis

Since the distribution of raw cortisol is typically skewed, and the normal diurnal profile may be approximated by an exponential curve, raw values were log-transformed.[2] Given the non-fixed time sampling protocol, cortisol levels were calculated at fixed times (8, 15 and 22 h) from the regression of the three-cortisol values on the sampling times, for each subject and on two different days (basal and stressful situation). Area under the curves (AUC) were also standardized and calculated between 08 and 22 h for each subject (extrapolating values from the equation of the regression line) as described previously (Chaudieu et al., 2008). Group comparisons were carried out using Student's *t*-test and analysis of variance for categorical explanatory variables. Individual stress responses, comparing home and hospital cortisol values, were performed using paired *t*-tests. *p*-values <0.05 were considered to be statistically significant. Data were analyzed using SAS version 9.1 (Cary, NC).

3. Results

The socio-demographic and clinical characteristics of the 162 subjects are given in Table 1. The mean (SD) age was 72.8 (4.4). There was no effect of age (either as a continuous or categorical variable in three classes (65–69/70–75/>75) on cortisol parameters. The participants selected for this study had no current MD and were not taking antidepressants. The level of current depressive symptomatology was low as attested by the CESD score. The lifetime prevalence of psychiatric disorders was relatively high in this elderly population, 15.4% of persons having reported MD and 25.3% anxiety disorder. Among the subjects with a history of MD, 44% reported two or three episodes. Median age of onset of MD was 49.5 years and the last depressive episode occurred several years before the cortisol sampling (median time 19.5 years).

[2] An absolute difference (δ) between two LnC values thus corresponds to a $(e^{\delta} - 1) \times 100$ variation (expressed as %) on initial (non-log-transformed) cortisol concentrations.