Research report

Age effects on cortisol levels in depressed patients with and without comorbid post-traumatic stress disorder, and healthy volunteers

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Abstract

Background: Post-traumatic stress disorder (PTSD) and major depression are frequently comorbid. Age and major depression are associated with higher cortisol levels and dexamethasone resistance, whereas PTSD is associated with lower cortisol and dexamethasone supersensitivity. Therefore, we examined the effect of age on the hypothalamic–pituitary–adrenal (HPA) system in depressed patients with and without PTSD. Methods: Thirty-one depressed patients without PTSD, 12 depressed patients with PTSD, and 23 healthy volunteers were studied on 2 days. Subjects received single-blind placebo on day 1 and fenfluramine on day 2. Cortisol levels were drawn before challenge and for 5 h thereafter. Results: Cortisol levels increase with age in depressed patients without PTSD but not in depressed patients with PTSD or in healthy volunteers. Number of previous major depressive episodes was a predictor of the cortisol response to fenfluramine administration in depressed patients without PTSD. Conclusions: The results of our study highlight the importance of considering age in psychobiology. Further research is needed to fully delineate the role of age in abnormalities of the HPA axis found in major depression and PTSD.

Keywords: Age; Depression; Post-traumatic stress disorder; Cortisol; Fenfluramine

1. Introduction

Major depression and post-traumatic stress disorder (PTSD) are common psychiatric disorders (Blazer et al., 1994; Breslau et al., 1991; Davidson et al., 1991). The National Comorbidity Survey estimates overall lifetime prevalence of major depressive disorder as 17.1% (Blazer et al., 1994). PTSD affects 9% of the population (Breslau et al., 1991), and if one adds subthreshold cases, the combined prevalence amounts to approximately 14–15% (Davidson et al., 1991).

PTSD and depression are frequently comorbid (Bleich et al., 1997; Kessler et al., 1995). Comorbidity between depression and PTSD is associated with greater symptom severity and higher risk for suicidal behavior (Oquendo et al., 2003a).

Both major depression (for review, see Holsboer, 2000) and PTSD (for review, see Yehuda, 2002) are associated with hypothalamic–pituitary–adrenal
(HPA) axis abnormalities. Oquendo et al. (2003b) has recently reported lower HPA activity in patients with comorbid PTSD and major depression.

Some early studies of HPA function in psychiatric patients suggested that aging did not substantially affect the HPA system (Carroll et al., 1981; Schlesser et al., 1980). Subsequently, that view changed. There is an increase in dexamethasone resistance with aging in depressed patients (Akil et al., 1993; Alexopoulos et al., 1984; Asnis et al., 1981; Brown et al., 1988; Halbreich et al., 1984; Lewis et al., 1984; Oxenkrug et al., 1983; von Bardeleben and Holsboer, 1991; Whiteford et al., 1987). There is disagreement about an age effect in healthy subjects (Ferrari et al., 2001; Parnetti et al., 1990; Ramasubbu et al., 2000; Sherman et al., 1985; von Bardeleben and Holsboer, 1991; Wilkinson et al., 2001). A recent study suggests that there is no difference in HPA activity in older and younger subjects with PTSD (Yehuda et al., 2002). We define aging as the gradual changes in the structure and function of humans that occur with the passage of time. In this study we focused on age, as an important variable that affects HPA axis function. Because the changes in the HPA system that are associated with aging and depression are opposite to those observed in PTSD, and because PTSD is often comorbid with major depression (Kluznik et al., 1986; Tennant et al., 1997), we examined the effect of age on the HPA system in depressed patients with and without PTSD. We hypothesized that age would affect HPA function in depressed patients without PTSD but not in depressed patients with PTSD. Measurement of cortisol levels following ingestion of fenfluramine, a specific serotonin releaser/uptake inhibitor agent, provides an index of HPA activity. We used this measurement to compare HPA activity in three groups: depressed subjects without a history of PTSD, depressed subjects with a history of PTSD, and healthy controls. To our knowledge, this is the first study of the effect of age on the HPA axis in depressed patients with comorbid PTSD.

2. Methods

2.1. Subjects

Participants were recruited through advertising and referrals and admitted to a university hospital for participation in mood disorders research. Thirty-one unipolar depressed patients without comorbid PTSD, 12 depressed subjects with comorbid PTSD, and 23 healthy volunteers entered the study. Patients were diagnosed based on the Structured Clinical Interview for DSM-III-R, patient version (SCID-P) (American Psychiatric Association, 1987). Diagnostic evaluations were performed by research psychologists and psychiatrists. All patients were medication free for a minimum of 14 days (6 weeks in the case of fluoxetine and 1 month in the case of oral antipsychotics) prior to study. Patients were allowed up to 3 mg daily of lorazepam during the washout phase, but not in the 3 days prior to the study. Healthy volunteers were recruited through advertising and were free of psychiatric diagnoses based on the non-patient version (SCID-NP). All subjects were free of medical illnesses based on history, physical examination and laboratory tests. Pregnant females were excluded. Pre-menopausal female subjects were studied within 5 days after onset of menses. All subjects gave written informed consent as approved by the Institutional Review Board. Demographic information was collected on the Columbia Baseline Demographic Form. Depressive symptoms were rated with the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and the Beck Depression Inventory (BDI) (Beck et al., 1961). Current hopelessness was measured with the Beck Hopelessness Scale (Beck et al., 1974). Most cases included in this study have been previously reported by Oquendo et al. (2003b).

2.2. Plasma cortisol studies

Subjects had studies on 2 consecutive days after fasting from midnight and throughout the test. They received placebo on the first day and fenfluramine on the second day in a single blind design. On each day, an intravenous catheter was inserted at approximately 08:00 h and an infusion of 5% dextrose and 0.45% saline was started. Cortisol levels were drawn 15 min and immediately before placebo or fenfluramine administration to ascertain baseline levels. An oral dose of approximately 0.8 mg/kg of DL-fenfluramine (or identical pill containing placebo) was administered at 09:00 h. Cortisol, fenfluramine and norfenfluramine levels were drawn hourly for 5 h thereafter. Subjects were awake during the procedure. Cortisol levels were
ascertained by radioimmunoassay (Vecsei, 1979) after denaturation of the binding proteins by heat. Anti-rabbit globulin serum, in conjunction with polyethylene glycol, was used for separation of the bound and free fractions. All samples were assayed in duplicate. The inter-assay coefficient of variation was 6.0%, 3.9% and 2.9% at concentrations of 3.1, 19.3 and 32.7 µg/dl, respectively. Fenfluramine and norfenfluramine levels were measured by a gas–liquid chromatography method (Krebs et al., 1984).

2.3. Statistical analysis

Response to fenfluramine administration was measured by the difference between the maximum of hourly plasma cortisol measurements following fenfluramine administration, and the baseline level measured 15 min before fenfluramine administration. Overall cortisol level was computed as the area under the curve of hourly cortisol measurements separately for the placebo day and the fenfluramine challenge day. To study the effect of age, separate linear regression models were fit for each of the three cortisol measures (baseline cortisol and the two listed above) measures listed above, for each of the three subject groups (healthy volunteers, depressed patients with and without PTSD). There was no evidence of non-linear relationship for any of the above variables. Drug levels were calculated as the sum of fenfluramine and norfenfluramine blood levels at each hour, and the maximum value of the hourly sums of the levels of the two drugs were compared. The clinical/ demographic characteristics of the three subject groups were compared using chi-square ($\chi^2$) tests of independence or analysis of variance.

3. Results

3.1. Clinical and demographic data

Data are provided in Table 1. The three groups, depressed patients with and without PTSD and healthy volunteers, did not differ with regard to age, race, marital status, or income. The percentage of females was higher among depressed subjects with PTSD than in the other two groups. The depressed subjects with PTSD had fewer years of education than the other two groups. Prevalence of reported childhood abuse was higher in depressed patients with PTSD. There was also a trend towards higher prevalence of subjects with psychomotor agitation among depressed patients with

<table>
<thead>
<tr>
<th>Variable name</th>
<th>Controls mean ± S.D. (%)</th>
<th>Patients without PTSD, mean ± S.D. (%)</th>
<th>Patients with PTSD, mean ± S.D. (%)</th>
<th>F or ($\chi^2$)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40.9 ± 16.7</td>
<td>42.3 ± 13.1</td>
<td>32.6 ± 7.9</td>
<td>2.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>60.9/39.1%</td>
<td>58.1/41.9%</td>
<td>83.9%</td>
<td>10.2</td>
<td>0.006&lt;sup&gt;ab&lt;/sup&gt;</td>
</tr>
<tr>
<td>Race (% white)</td>
<td>73.9%</td>
<td>83.9%</td>
<td>58.3%</td>
<td>3.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Marital status (married/unmarried)</td>
<td>65.2/34.8%</td>
<td>41.7/58.3%</td>
<td>48.4/51.6%</td>
<td>2.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Years of education</td>
<td>16.8 ± 2.2</td>
<td>16.2 ± 2.2</td>
<td>13.8 ± 2.1</td>
<td>7.7</td>
<td>&lt;.001&lt;sup&gt;ab&lt;/sup&gt;</td>
</tr>
<tr>
<td>Income ($ \times 10^3$)</td>
<td>28.6 ± 29.4</td>
<td>23.9 ± 21.8</td>
<td>14.8 ± 15.3</td>
<td>1.3</td>
<td>0.3</td>
</tr>
<tr>
<td>HDRS</td>
<td>1.3 ± 1.9</td>
<td>19.4 ± 4.9</td>
<td>20.8 ± 6.3</td>
<td>131.6</td>
<td>&lt;.0001&lt;sup&gt;ac&lt;/sup&gt;</td>
</tr>
<tr>
<td>Beck Depression Scale</td>
<td>1.8 ± 3.7</td>
<td>27.5 ± 8.6</td>
<td>32.2 ± 11.7</td>
<td>86.6</td>
<td>&lt;.0001&lt;sup&gt;ac&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hopelessness Scale</td>
<td>1.7 ± 1.7</td>
<td>12.1 ± 4.4</td>
<td>14.3 ± 5.8</td>
<td>56.0</td>
<td>&lt;.0001&lt;sup&gt;ac&lt;/sup&gt;</td>
</tr>
<tr>
<td>Presence of a history of childhood abuse</td>
<td>N/A</td>
<td>26.7%</td>
<td>81.8%</td>
<td>10.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Presence of melancholia</td>
<td>N/A</td>
<td>22.6%</td>
<td>33.3%</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Presence of psychomotor agitation</td>
<td>N/A</td>
<td>3.2%</td>
<td>25%</td>
<td>4.9</td>
<td>0.06</td>
</tr>
<tr>
<td>Presence of delusions</td>
<td>N/A</td>
<td>9.7%</td>
<td>8.3%</td>
<td>0.02</td>
<td>0.9</td>
</tr>
</tbody>
</table>

<sup>a</sup> Controls are different from depressed patients with PTSD at 0.05.
<sup>b</sup> Depressed patients without PTSD are different from depressed patients with PTSD at 0.05.
<sup>c</sup> Controls are different from depressed patients without PTSD at 0.05.
PTSD compared to depressed patients without PTSD. Severity of depression as measured by HDRS and BDI, current hopelessness, and prevalence of subjects with delusions and melancholia were not different between the two depressed groups.

3.2. Cortisol levels

On the placebo day, cortisol levels in depressed patients without PTSD increased with age (df = 1,25, \( F = 7.6, P = 0.01 \)). This effect was not present in depressed patients with PTSD (df = 1,10, \( F = 0.1, P = 0.7 \)) and in healthy volunteers (df = 1,20, \( F = 0.15, P = 0.7 \)). On the fenfluramine day, there was a trend towards an increase in cortisol levels with age in depressed patients without PTSD (df = 1,27, \( F = 3.2, P = 0.09 \)). Age did not affect cortisol levels on the fenfluramine day in depressed patients with PTSD (df = 1,10, \( F = 0.2, P = 0.7 \)) and in healthy volunteers (df = 1,20, \( F = 0.2, P = 0.7 \)). We found no correlations between psychological parameters (severity of depression as measured by HDRS and BDI and current hopelessness) and cortisol levels on either day. There were no gender differences in cortisol levels with and without fenfluramine.

3.3. Cortisol response to fenfluramine administration

Age, gender, severity of depression as measured by HDRS and BDI, presence of childhood history of abuse, delusions and melancholia were found not to be predictors of baseline or post-challenge plasma cortisol in any of the three groups. There was a significant increase in cortisol after fenfluramine administration in depressed patients without PTSD (df = 28, \( t = 2.55, P = 0.02 \)) and in healthy volunteers (df = 20, \( t = 2.9, P = 0.008 \)). There was no response to fenfluramine administration in depressed subjects with PTSD (df = 10, \( t = 0.8, P = 0.5 \)).

We found no group differences in plasma cortisol responses to fenfluramine (df = 2,62, \( F = 0.3, P = 0.8 \)) or in baseline cortisol levels (df = 2,62, \( F = 0.8, P = 0.5 \)). There were no group differences in fenfluramine plus norfenfluramine levels (df = 2,62, \( F = 2.4, P = 0.1 \)). The number of previous major depressive episodes did not predict the baseline cortisol level in depressed subjects with PTSD (df = 1,28, \( F = 0.7, P = 0.4 \)). However, the number of previous major depressive episodes was a predictor of the cortisol response to fenfluramine administration in depressed subjects without PTSD (df = 1,28, \( F = 5.7, P = 0.02 \)). Relationship of cortisol to the number of previous depressive episodes remained significant after controlling for age (df = 1,27, \( F = 6.0, P = 0.02 \)).

4. Discussion

4.1. Age effects in depressed patients without comorbid PTSD

We found that cortisol levels in depressed patients without PTSD increased with age. Our finding is consistent with the view that glucocorticoid feedback through both corticosteroid receptors types is less responsive over succeeding episodes of major depression. This effect is apparently aggravated by increasing age. This is not a simple aging effect because it is absent in healthy volunteers. The potentiating or additive effect of age in conjunction with depression on pituitary adrenocortical activity was suggested by other studies. Mean 24-h cortisol level increases with age in depression (Halbreich et al., 1984). Elderly depressives who are cortisol non-suppressors after dexamethasone need more time for pituitary adrenocortical normalization to occur than younger subjects (Greden et al., 1986). An increase in post-dexamethasone cortisol levels with age has been reported in major depressive disorder (Whiteford et al., 1987). A significant effect of age on cortisol release in depressed patients has been observed during the combined dexamethasone–corticotropin-releasing hormone test: older patients had higher post-dexamethasone cortisol levels (Von Bardeleben and Holsboer, 1991). In patients with endogenous depression advancing age leads to higher baseline cortisol and a greater likelihood of being a dexamethasone non-suppressor (Akil et al., 1993). Others report similar observations (Alexopoulos et al., 1984; Asnis et al., 1981; Brown et al., 1988; Lewis et al., 1984; Oxenkrug et al., 1983).

4.2. Number of previous depressive episodes and cortisol response

Our finding that the number of previous major depressive episodes was a predictor of a cortisol
response to fenfluramine administration in depressed patients without PTSD is in agreement with the hypothesis that stress during recurrent depressive episodes results in cumulative hippocampal injury, and consequently, impairment of this HPA axis feedback pathway (Sheline et al., 1999). Hippocampal volume loss has been associated with both depression (Sheline et al., 1996; Sheline et al., 1999) and aging (Jemigan et al., 1991). Prolonged exposure to elevated levels of glucocorticoids associated with major depression may be neurotoxic and reduces hippocampal cell number (Sapolsky et al., 1985). Corticosteroids induce cultured neurons to undergo apoptosis (Reagan and McEwen, 1997). Although both aging (Jemigan et al., 1991; Landfield et al., 1981; Lupien et al., 1998; Sheline et al., 1999) and depression-related neurotoxic exposure (Sheline et al., 1996; Sheline et al., 1999) may produce loss of vulnerable hippocampal neurons, the combination of neurotoxic exposure and aging may have a synergistic effect through enhanced vulnerability to cell damage (Sapolsky, 1992).

4.3. Age effects in depressed patients with comorbid PTSD

We found that age did not affect cortisol levels in depressed patients with PTSD. Our finding is in agreement with a recent report by Yehuda et al. (2002) that suggests that the response to dexamethasone is generally similar in older and younger trauma survivors. Our finding is also consistent with the view that alterations in the HPA system associated with aging and depression are generally opposite of those observed in PTSD (Yehuda et al., 2002). The majority of studies of PTSD show alterations consistent with the enhanced negative feedback inhibition of cortisol on the pituitary and an overall hyperactivity of other target tissues (adrenal gland, hypothalamus) (for review, see Yehuda, 2002). For example, many studies found a greater cortisol suppression following dexamethasone administration in subjects with PTSD compared to similarly exposed or non-trauma exposed subjects (Goenjian et al., 1996; Halbreich et al., 1989; Heim et al., 1998; Stein et al., 1997; Yehuda et al., 1993; Yehuda et al., 1995). A number of studies reported lower plasma or 24-h urine cortisol in subjects with PTSD compared with normal controls (Heim et al., 2001; Kellner et al., 2000; Yehuda et al., 1990), or depressed patients (Mason et al., 1986; Yehuda et al., 1996). It appears that the HPA changes associated with PTSD may “neutralize” the HPA alterations associated with aging and depression.

4.4. Age effects in healthy volunteers

We found that age did not affect cortisol levels in healthy volunteers. Our observation is consistent with reports by Sherman et al. (1985); von Bardeleben and Holsboer (1991); Ramasubbu et al. (2000). The 24-h mean cortisol concentration and the number of cortisol peaks as well as their amplitude and duration were studied in healthy volunteers and no difference between younger and older subjects was found (Sherman et al., 1985). No difference in the results of combined dexamethasone–corticotropin-releasing hormone test was found between younger and older healthy volunteers (von Bardeleben and Holsboer, 1991). A recent study suggests that aging has no effect on cortisol responses to fenfluramine administration in healthy elderly subjects (Ramasubbu et al., 2000). However, a number of authors suggest that age affects HPA regulation in humans (Ferrari et al., 2001; Panetti et al., 1990; Wilkinson et al., 2001). Differences in the results of studies may be explained by differences in a sample size, screening criteria, and some other factors, such as differences in sleeping patterns (Aeschbach et al., 2003). Given the flexibility of the HPA system and the multiplicity of its checks and balances, it is not unexpected that multiple patterns of responses appear to emerge across subjects.

5. Conclusion

Our findings highlight the importance of considering age in psychobiology. The association among depression, PTSD, aging, and HPA function has many implications for understanding and management of depression and PTSD, since each level involved in regulation of the HPA system is also involved in many other aspects of adaptation to various stressors. Further research is needed to fully delineate the role of age in abnormalities of the HPA axis found in depression without PTSD. It is unclear why PTSD seems to protect against aging.
effects on the HPA axis and this worthy of further study.

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References


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