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Preliminary communication

Effects of chronic prednisone therapy on mood and memory

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Abstract

Background: In animals, stress and corticosteroids can be associated with both reversible and irreversible changes in the hippocampus. Changes in memory and hippocampal structure, perhaps in part due to cortisol elevations, are reported in some patients with mood disorders. Minimal data are available on the effects of long-term exposure to corticosteroids on the human hippocampus. We previously reported greater depressive symptom severity, poorer memory and smaller hippocampal volumes in patients with asthma or rheumatic diseases receiving long-term prednisone therapy than in controls.
Methods: In this report, patients and controls were assessed a mean of 4 years after the first assessment to determine if depressive and manic symptoms and cognition remained stable, improved or worsened. Seven prednisone-treated patients and six controls were identified and agreed to reassessment with psychiatric symptom and neurocognitive measures. Follow-up MRIs for hippocampal volume analysis were available for two prednisone-treated participants.
Results: With the exception of an increase in depressive symptoms in those receiving prednisone, participants and controls did not show significant change in mood or cognition from the initial assessment. One participant discontinued prednisone and showed improvement in psychiatric symptoms and cognition. Hippocampal volumes were available in two prednisone-treated participants and showed inconsistent findings.
Limitations: A limitation is the small sample size.
Conclusions: Our findings, although preliminary in nature, suggest that long-term prednisone therapy is associated with initial changes in mood, memory and hippocampal volume that appear to stabilize over time.

Keywords: Hippocampus; Corticosteroids; Memory; Prednisone; Depression

1. Introduction

In animal models, stress and corticosteroids are associated with memory impairment and reversible and irreversible hippocampal changes (McEwen, 2000). Humans exposed to an excess of cortisol or exogenous corticosteroids also show hippocampal changes and cognitive impairment (Brown et al., 2004; Starkman et al., 1992). Changes in mood (Brown et al., 2002; Naber et al., 1996) and declarative memory (Brown et al., 2006; Brunner et al., 2005; Newcomer et al., 1999) are reported even during brief exposure to exogenous corticosteroids.

A prior report compared a group of 17 corticosteroid-dependent patients (mean dose 15.6 mg/day of prednisone, mean duration 92.0 months) with asthma or

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rheumatic illnesses with 15 controls with similar demographic characteristics and medical histories but with minimal lifetime corticosteroid use (Brown et al., 2004). Compared to controls, the corticosteroid-treated group had poorer performance on the Rey Auditory Verbal Learning Test (RAVLT), a measure of declarative memory (hippocampal) performance, the Stroop Color Word Test, a measure of working memory (prefrontal cortex) performance, smaller hippocampal volumes, lower levels of *N*-acetyl aspartate, a putative marker of neuronal viability in the temporal lobe region, and greater depressive symptom severity.

These findings may be applicable to patients with major depressive disorder. A subset of depressed patients has elevated cortisol or a frequently associated finding of non-suppression on the dexamethasone test (Arana et al., 1985). In addition, some studies of patients with major depressive disorder report hippocampal atrophy compared to controls (Sheline et al., 1996).

In this report we conducted a follow-up study of corticosteroid-dependent patients and controls from two previous studies who received mood, cognitive and, in some cases, structural MRI assessments at baseline (Brown et al., 2003; Brown et al., 2004). We re-examined mood and cognition and, in two cases, hippocampal volume at follow-up to determine if mood, cognition and hippocampal volume remained stable over time.

2. Methods

Methods of the original studies, including neuroimaging techniques, are described in detail in Brown et al. (2003, 2004). To summarize, in one study (Brown et al., 2004) 17 adult outpatients with asthma or rheumatologic diseases who were receiving chronic prednisone therapy and 15 controls with similar medical histories but with minimal lifetime corticosteroid exposure were enrolled. Exclusion criteria included lifetime posttraumatic stress disorder, schizophrenia, major depressive disorder or bipolar disorder, substance abuse/dependence, illnesses with significant neurological manifestations and contraindications to MRI. Participants were assessed with the Structured Clinical Interview for DSM-IV (First et al., 1995), Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960), Young Mania Rating Scale (YMRS) (Young et al., 1978), Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), neurocognitive tests that included the Rey Auditory Verbal Learning Test (RAVLT) (Schmidt, 1996) and Stroop Color Word Test-Victoria version (Spreen and Strauss, 1998), and structural MRI and ^{1}H magnetic resonance spectroscopy of the brain.

In a separate study, a similar baseline assessment, except without imaging, was performed in 10 corticosteroid-dependent patients who were enrolled in a 12-week trial of lamotrigine (Brown et al., 2003). Inclusion criteria were virtually identical to the study described above (Brown et al., 2004). Four of the participants also participated in the imaging study described above (Brown et al., 2004) leaving six additional participants. For the present analysis, assessment scores for these participants were combined with those from the study described above to increase the sample of prednisone-treated patients for follow-up analysis.

IRB approval was obtained to contact the former participants from both studies for a follow-up assessment. Written informed consent was obtained. The total number of potential participants was 23 on corticosteroid therapy and 15 controls. Of these 38, 13 participated in the re-assessment, 17 could not be reached or had moved out of the area, 1 was deceased and 7 declined to participate. Of the 7 who declined to participate, 4 stated work schedule conflicts or transportation difficulties as the reason, while the remainder did not give a reason for the decision.

In the 13 follow-up participants, the HRSD, YMRS, BPRS, RAVLT, and Stroop Color Word Task were administered. In addition, as part of a baseline assessment for another study, we were able to obtain follow-up MRIs on two of the participants. Mood and cognitive assessments were performed by a research assistant who was blinded to participant treatment status. Hippocampal volumes were measured by the same blinded rater (DJW) as in the original study.

2.1. Statistical analysis

Independent *t*-tests for continuous measures or Chi Square tests for discrete measures were used to examine participant characteristics. Psychiatric symptoms and cognition were assessed between groups using independent 2-sided *t*-tests and within groups using paired *t*-tests. Significance was set at $p \leq 0.05$ for all analyses. Cognitive data are reported as normative values (*t*-scores) that control for age. Statistical analyses were performed using SPSS Version 13.0.

3. Results

Demographic characteristics of the patients and controls are given in Table 1. The group receiving prednisone and controls only differed significantly on education, although a substantial, but not statistically significant, difference in age was observed. Participants