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Research Paper

Interferon-alpha-induced inflammation is associated with reduced glucocorticoid negative feedback sensitivity and depression in patients with hepatitis C virus

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HIGHLIGHTS

- IFN-alpha decreased glucocorticoid sensitivity in association with flattened diurnal cortisol slope in patients with hepatitis C virus
- Decreased glucocorticoid sensitivity was correlated with increased IFN-alpha-induced soluble tumor necrosis factor receptor 2 (sTNFR2)
- Increased sTNFR2 predicted increased depression and fatigue scores, independent of the change in glucocorticoid sensitivity
- Inflammation in medical illness may decrease glucocorticoid sensitivity, in turn increasing cytokines and their effects on behavior

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ABSTRACT

Major medical illnesses are associated with increased risk for depression and alterations in hypothalamic–pituitary–adrenal (HPA) axis function. Pathophysiological processes such as inflammation that occur as a part of medical illnesses and their treatments have been shown to cause depressive symptoms, and may also affect the HPA axis. We previously reported that patients with hepatitis C virus chronically administered interferon (IFN)-alpha develop increased evening plasma cortisol concentrations and a flattened diurnal cortisol slope, which correlated with increased tumor necrosis factor (TNF) and its soluble receptor 2 (sTNFR2). Increased TNF and sTNFR2 were further correlated with depression and fatigue scores. The current study examined whether flattened cortisol slope might be secondary to reduced glucocorticoid receptor (GR) sensitivity, by measuring glucocorticoid negative feedback to dexamethasone (DEX) administration followed by corticotropin releasing hormone (CRH) challenge. In an exploratory analysis, 28 male and female patients with hepatitis C virus were studied at baseline (Visit 1) and after 12 weeks (Visit 2) of either IFN-alpha plus ribavirin ($n = 17$) or no treatment ($n = 11$). Patients underwent dexamethasone DEX–CRH challenge, neuropsychiatric assessments, and measurement of plasma TNF and sTNFR2 during each visit. IFN-alpha did not affect neuroendocrine responses following CRH but did increase post-DEX cortisol, which was correlated with flattening of the diurnal cortisol slope ($r = 0.57$, $p = 0.002$) and with increased depression scores ($r = 0.38$, $p = 0.047$). Furthermore, the change in post-DEX cortisol was associated with IFN-alpha-induced increase in sTNFR2 ($r = 0.51$, $p = 006$), which was in turn correlated with depression ($r = 0.63$, $p < 0.001$) and fatigue ($r = 0.51$, $p = 0.005$) scores. Whereas the relationship between sTNFR2 and depression scores were independent of the change in post-DEX cortisol, the correlation between post-DEX cortisol and depression scores was not significant when controlling for sTNFR2. These findings suggest that inflammation induced in patients with hepatitis C virus during IFN-alpha therapy precipitates decreased GR sensitivity to lead to a flattened diurnal cortisol slope. Decreased GR sensitivity may in turn further increase inflammation and its ultimate effects on behavior. Treatments that target inflammation and/or GR sensitivity may reduce depressive symptoms associated with medical illnesses.

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Contents

1. Introduction

Medical illnesses such as chronic viral infections, cancer and cardiovascular disease are associated with increased risk for depression as well as with changes in hypothalamic–pituitary–adrenal (HPA) axis function, including reduced glucocorticoid receptor (GR) sensitivity [1,12,36,53]. One pathophysiologic process that may account for relationships among medical illness, depression and HPA dysregulation is inflammation [20,55]. Increased inflammation has been observed in both medically ill and medically healthy patients with depression, and administration of inflammatory stimuli and cytokines to humans and laboratory animals causes depressive behaviors [10,23,35,46,65]. Indeed, administration of the inflammatory cytokine interferon (IFN)-alpha for malignant melanoma or hepatitis C virus (HCV) leads to a range of depressive symptom including anhedonia, anxiety, sleep disturbances and fatigue [17,48], all of which have been found to correlate with induction of other cytokines and inflammatory signaling pathways [13,14,42,50]. Similar relationships between inflammatory markers and depressive symptoms have been observed in other medical illnesses, particularly in cancer patients undergoing treatment with chemotherapy and radiation that, like IFN-alpha, activate endogenous production of inflammatory cytokines and gene expression pathways [3,5,61].

Medical illnesses such as cancer and the administration of IFN-alpha have also been associated with changes in HPA axis function [1,29,45,51,53,59]. For example, women with breast cancer have been found to exhibit higher blood cortisol concentrations following oral dexamethasone administration, which correlated with a more flattened cortisol slope [58]. Moreover, administration of IFN-alpha caused flattened cortisol slope and increased evening cortisol concentrations in patients with hepatitis C virus, both of which correlated with depression and fatigue scores. Depression and fatigue scores were in turn positively correlated with induction of the inflammatory cytokine tumor necrosis factor (TNF) and its soluble receptor 2 (sTNFR2) [45].

A number of studies have indicated that a flattened cortisol slope is associated with increased morbidity and mortality in the context of a variety of illnesses including diabetes, cardiovascular disease and cancer [1,29,51,52,59]. The mechanism of this altered diurnal cortisol rhythm in inflammation-related illness is unknown, although data suggests that changes in GR sensitivity may be involved [37]. In the current study, we examined whether the flattened cortisol slope in patients with hepatitis C virus administered IFN-alpha may occur secondary to alterations in glucocorticoid negative feedback sensitivity as measured by the dexamethasone (DEX) suppression test followed by administration of corticotropin releasing hormone (CRH) (the DEX–CRH challenge) [21,22], and whether changes in sensitivity to DEX were associated with previously described IFN-alpha-induced increases in plasma TNF and sTNFR2 and depressive behaviors [45].

2. Methods and materials

2.1. Participants

Twenty-eight HCV-positive subjects (14 males, 14 females) were enrolled. Exclusion criteria included decompensated liver disease; liver disease from any cause other than HCV; unstable cardiovascular, endocrinologic, hematologic, renal or neurologic disease (as determined by physical exam and laboratory testing); infection with HIV (as reported by the subjects' treating physician); and history of schizophrenia or bipolar disorder and/or a diagnosis of major depression or substance abuse/dependence within 6 months of study entry, as determined by Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition [18]. Patients were required to be off all antidepressant, antipsychotic, or mood stabilizer medications for at least 4 weeks prior to study entry (8 weeks for fluoxetine). Subjects were also required to discontinue other agents that might affect study results (i.e., narcotic analgesics, benzodiazepines, and anti-inflammatory agents) at least 2 weeks prior to sample collection. The subjects reported on herein represent a subsample of subjects included in previous studies on the effects of IFN-alpha on depressive behaviors, cognitive performance, neuroendocrine function, gene expression, and inflammatory responses [13,16,43,45,47,15]. All subjects provided written informed consent, and study procedures were approved by the Emory University Institutional Review Board.

2.2. Study design

Study participants were enrolled in a longitudinal study examining immune, neuroendocrine, and neuropsychiatric variables at baseline and after either no treatment or chronic treatment with IFN-alpha/ribavirin [13,14,16,44,45,47]. For purposes of this study, DEX–CRH challenge involved administration of DEX at 2300 h followed by collection of 6 post-DEX cortisol and adrenocorticotropic hormone (ACTH) samples from 1230 to 1300 h the following day (DEX suppression test) prior to administration of CRH and collection of 6 subsequent samples over 2 h (CRH challenge) as previously described [21,22]. The DEX–CRH challenge was performed at baseline (Visit 1) and at 12 weeks (Visit 2) from a subset of HCV + patients treated with IFN-alpha plus ribavirin ($n = 17$) or untreated HCV + patients awaiting IFN-alpha/ribavirin

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