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Depressive symptoms and the regulation of proinflammatory cytokine expression in patients with coronary heart disease☆

Gregory E. Miller[a,*], Kenneth E. Freedland[b], Robert M. Carney[b]

[a]*Department of Psychology, University of British Columbia, 2136 West Mall, Vancouver BC, Canada V6T 1Z4*
[b]*Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, United States*

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Abstract

Objective: Depressive symptoms increase the risk of morbidity and mortality in patients with coronary heart disease (CHD). Mounting evidence indicates that inflammatory processes may underlie this association. This study examined whether depressive symptoms are associated with the dysregulation of inflammatory cytokine production in response to an in vitro infectious challenge. **Methods:** Forty-one patients with CHD were enrolled 3 months or more after an acute myocardial infarction or revascularization procedure. Depressive symptoms were assessed through self-report and interviewer ratings. Cytokine production was measured after white blood cells were cultured in vitro with endotoxin in the presence of varying concentrations of dexamethasone. **Results:** Depressive symptoms were not associated with the quantity of in vitro inflammatory cytokine production. However, to the extent that they reported symptoms of depression, patients showed greater sensitivity to the anti-inflammatory properties of glucocorticoids. This was manifested by increased suppression of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) production by dexamethasone. **Conclusions:** Increased sensitivity to glucocorticoid inhibition could render depressed patients vulnerable to latent infections and inflammatory processes that accelerate the progression of cardiac disease.

Keywords: Depression; Inflammation; Cytokine; Cortisol; Coronary disease

Introduction

Coronary heart disease (CHD) is frequently accompanied by symptoms of depression. Recent evidence indicates that 17–27% of CHD patients suffer from comorbid major depression, and at least as many patients have subsyndromal depressive symptoms [1]. Depressive symptoms markedly diminish the quality of life of CHD patients [2], and they also may contribute to poor medical outcomes [3,4]. Patients who are depressed following a myocardial infarction, for example, have a two- to fourfold increased risk of cardiac morbidity and mortality [1,5,6]. In some studies, the prognostic significance of this effect has been comparable with that of left ventricular dysfunction and previous myocardial infarction [5,6].

The mechanisms responsible for this phenomenon are not well understood. A number of researchers have advanced the hypothesis that depressive symptoms accelerate the progression of atherosclerosis by fostering latent or chronic infections and activating inflammatory processes [7-10]. Initial support for this hypothesis has emerged in studies of medically healthy adults [11–14] and in studies of patients with coronary artery disease. For example, in a small cohort of patients undergoing percutaneous transluminal angioplasty, Appels et al. [8] found that major depression was associated with higher rates of latent infection with cytomegalovirus and chlamydia pneumoniae, as well as elevated concentrations of interleukin-1β (IL-1β) and tumor

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* Corresponding author. Tel.: +1 604 822 3269; fax: +1 604 822 6923.
E-mail address: gemiller@psych.ubc.ca (G.E. Miller).

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necrosis factor-α (TNF-α). In a large study of patients recovering from acute coronary syndromes, Lespérance et al. [15] found that major depression was associated with increased levels of C-reactive protein (CRP) and soluble intercellular adhesion molecule-1 (sICAM-1), which are markers of systemic inflammation and endothelial activation, respectively. We recently studied a cohort of 65 patients recovering from acute coronary syndromes and found that depressive symptoms were accompanied by increases in both pathogen burden and systemic inflammation. These effects were fairly large: Patients in the highest tertile of depressive symptoms had a median CRP value 50% higher than that of patients in the middle and lowest tertiles. Moreover, 100% of patients in the highest tertile were latently infected with atherogenic pathogens; the comparable values in the middle and lowest tertiles were 55% and 43%, respectively [16].

This pattern of findings suggests that the immune response is dysregulated in cardiac patients who report depressive symptoms. However, the specific immune system processes that go awry in these patients have not yet been characterized. The present study examined whether depressive symptoms influence a basic immune system process, the ability to produce inflammatory cytokines in response to an in vitro infectious challenge. Inflammatory cytokines are a critical element of the host response to invading microorganisms and must be produced in a timely and sufficient fashion if the pathogen is to be eradicated. Once this has been accomplished, however, the immune response must be terminated. Glucocorticoid hormones are one of the body's mechanisms for regulating inflammation and halting the white blood cell response to invading pathogens [17]. If white blood cells become overly sensitive to the actions of glucocorticoids, they may down-regulate inflammatory response prematurely, before the pathogens have been cleared. If they become resistant to glucocorticoids, however, the immune response may continue unchecked and exacerbate inflammatory conditions [18,19]. Given the critical role that this regulatory circuit plays in governing immune responses, the present research also sought to determine whether it is disrupted in cardiac patients who endorse depressive symptoms [7,20]. We did this by determining whether depressive symptoms influence white blood cells' capacity to suppress inflammatory cytokine production when they are exposed to glucocorticoids in the context of an in vitro infectious challenge.

Methods

Sample

The sample consisted of 41 patients recruited from cardiology practices at Barnes-Jewish Hospital of Washington University School of Medicine. The patients were part of larger project on depression and disordered sleeping in cardiac disease. They had volunteered to be part of a substudy on immune processes (see Ref. [16]) and had sufficient blood drawn for us to perform glucocorticoid sensitivity assays. After providing written informed consent, potentially eligible patients underwent a medical history interview with a research nurse. Candidates were excluded if they were found to have (a) severe cognitive impairment, psychiatric conditions other than depression or anxiety, or excessive substance/alcohol use, (b) comorbid medical conditions including advanced malignancy, diabetic neuropathy, severe pulmonary disease, or a diagnosed sleep disorder, or (c) valvular heart disease, active congestive heart failure, or an implantable pacemaker. Patients who met the eligibility criteria were scheduled for a two-night stay at the Washington University Sleep Medicine Center. The Institutional Review Board of Washington University School of Medicine approved the protocol.

Depressive symptoms

Depressive symptoms were assessed by self-report and interviewer ratings. During their stay at the Sleep Medicine Center, patients completed the Beck Depression Inventory (BDI), a 21-item self-report inventory of depressive symptoms [21]. Interviewer ratings of depressive symptoms were obtained at the eligibility screening session, when the research nurse administered the 17-item Hamilton Rating Scale for Depression (HAM-D; [22]). Both the BDI and HAM-D showed high levels of internal consistency in this sample (αs=.94 and .89). Because scores on these measures were highly correlated (r=.89, P<.001), we z-transformed and averaged them to form an index reflecting the severity of depressive symptoms.

Immune response

The protocol for assessing the immune system's capacity to regulate cytokine production during infectious challenge has been used in previous research [23]. Within 1 h of waking at the Sleep Medicine Center, patients had 10 ml of blood drawn through antecubital venipuncture. Sometime in the next 2 h, the whole blood was diluted with saline 10:1 and then added to a 24-well flat-bottom plate in 800 μl aliquots. One hundred microliters of bacterial extract in the form of lipopolysaccharide (LPS; Sigma, St. Louis, MO) was then added to each well at a final concentration of 100 ng/ml. Next, 100 μl of the synthetic glucocorticoid dexamethasone (Sigma), dissolved in phosphate buffering solution (PBS), was added to each well. The dexamethasone was dissolved in varying quantities of PBS so that final in-well concentrations were 0, 1, 10, 50, 100, or 1000 nM. Samples were then incubated for 6 h at 37 °C with 5% CO_2. The plates were removed from the incubator and centrifuged for 10 min at 1000×g. Plasma samples were then aspirated and stored at −70 °C until the study was completed. The samples were thawed at that time, and the cytokines IL-1β,

IL-6, and TNF-α were measured using a fluorescence immunoassay (Linco Research, Saint Louis, MO) on a Luminex 100 Instrument (Austin, TX). These assays have a sensitivity of 3.2 pg/ml and intra- and interassay coefficients of variation <12%.

To prepare the data for statistical analysis, dose–response curves were generated for each patient. We then calculated the concentration of dexamethasone needed to diminish each patient's cytokine production by 50%. This value is called the inhibitory coefficient-50 (IC_{50}) and is widely used to model the potency of antagonist medications. IC_{50} calculations were performed in GraphPad Prism 3.02 (San Diego, CA). This software estimates the log IC_{50} (instead of the raw IC_{50}) because this value has superior statistical properties. Readers should note that log IC_{50} values are inversely proportional to glucocorticoid sensitivity. That is, higher IC_{50} values indicate that more dexamethasone is needed to suppress cytokine production by 50%, i.e., that the white blood cells are more resistant to the anti-inflammatory properties of glucocorticoids.

Potential confounds: disease, treatment, infection

Chart reviews and medical history interviews were utilized to gather data regarding potential confounding variables. These variables included demographic characteristics, medical history, and treatment regimens. To rule out acute infections as sources of variability in inflammatory processes, a complete blood count with differential was performed. Patients with serologic evidence of currently active infectious disease were excluded (white blood cell count $>10.8\times10^9$ cells/l; n=1).

Statistical analyses

Pearson's correlations were used to examine the relationships among depressive symptoms and cytokine production, and partial correlations were used to adjust for potential confounds. All statistical analyses utilized two-tailed tests of significance, with α set to .05. With these parameters and a sample of 41 patients, correlations exceeding r=.30 achieved statistical significance. The data are presented as mean±S.E.M. unless otherwise specified.

Results

Sample characteristics

The sample consisted of male (n=24, 58.5%) and female (n=17, 41.5%) patients who averaged 60.8 (S.E.M.=1.5) years of age. Most patients were of Caucasian descent (90.2%); although a small minority was African-American (9.8%). The sample contained roughly equal numbers of patients with a high school diploma or less (35.1%), some college education (24.3%), and a college diploma or greater (40.5%.) The majority of patients were married (73.2%). The rest were widowed (14.6%), separated/divorced (9.7%), or never married (2.4%).

Table 1 displays the psychiatric and medical characteristics of the sample. Patients' scores on the BDI and HAM-D indicate that they were, on average, experiencing depressive symptoms of mild–moderate severity. The majority of patients had a history of angina, hypertension, myocardial infarction, and/or revascularization.

To evaluate the psychometric characteristics of major study variables, we generated histograms and computed skew and kurtosis statistics. In each case, the values that emerged were ≤1.40, suggesting that indices of depressive symptoms, cytokine production, and glucocorticoid sensitivity were normally distributed in this sample of patients.

Depressive symptoms and cytokine production

The first wave of statistical analyses examined relations between depressive symptoms and the immune system's capacity to produce inflammatory cytokines during in vitro infectious challenge. These analyses focused on baseline production of cytokines, i.e., in cultures that were not treated with the anti-inflammatory dexamethasone. Depressive symptoms were not reliably associated with the extent of cytokine production. This was the case for IL-1β (r=−.16, P=.32), IL-6 (r=−.08, P=.64), and TNF-α (r=−.11, P=.51). These findings suggest that, in cardiac patients, depressive symptoms are unrelated to the ability to mount an inflammatory cytokine response to infectious challenge in vitro.

The next wave of analyses explored the immune system's capacity to regulate the production of inflammatory

Table 1
Medical and psychiatric characteristics of the sample

Variable	Mean±S.E.M. or percent
Depressive symptoms	
Beck Depression Inventory	14.9±1.8
Hamilton Rating Scale	11.3±1.3
Biological outcomes	
Interleukin-1β (log IC_{50})	1.4±.04
Interleukin-6 (log IC_{50})	1.7±.03
Tumor necrosis factor-α (log IC_{50})	1.7±.02
Medical history	
Diabetes (%)	24.4
Hypertension (%)	63.4
Angina pectoris (%)	65.9
Myocardial infarction (%)	48.8
Time since infarction (months)	21.5±7.9
Killip class (%) >1	0.0
Congestive heart failure (%)	17.1
Ventricular arrhythmia (%)	2.4
Peripheral vascular disease (%)	7.5
Cerebrovascular accident (%)	14.6
Angioplasty (%)	56.1
Bypass surgery (%)	36.6

cytokines after it has been activated. These analyses focused on how well dexamethasone suppresses cytokine production following infectious challenge. Depressive symptoms were inversely associated with IC_{50} values for IL-6 ($r=-.32$, $P<.04$) and for TNF-α ($r=-.36$, $P<.02$). These findings indicate, in samples drawn from patients with higher levels of depressive symptoms, that *smaller* concentrations of dexamethasone were needed to suppress cytokine production by 50%. Thus, depressive symptoms were associated with an enhanced sensitivity to the anti-inflammatory properties of glucocorticoids, i.e., a stronger tendency to suppress the immune response to in vitro stimulation. For IL-1β, the findings were in the same direction, but not statistically significant ($r=-.17$, $P=.28$).[1]

Because whole blood was used to measure glucocorticoid sensitivity, disparities in the cellular composition of the samples could have influenced the extent of cytokine production. The concentration of monocytes is the most critical factor, as these cells are the major immune system producers of inflammatory cytokines. However, adjustment for monocyte count did not diminish the relations between depressive symptoms and IC_{50} values for IL-6 (partial $r=-.32$, $P<.04$) or TNF-α (partial $r=-.37$, $P<.02$). These results indicate that the depression-related disparities in glucocorticoid sensitivity are not simply due to disparities in monocyte numbers.

Testing alternative explanations

The final wave of statistical analyses examined alternative explanations for the finding that depressive symptoms are associated with enhanced IL-6 and TNF-α glucocorticoid sensitivity. Patients who reported more severe depressive symptoms tended to be female [$t(39)=2.25$, $P<.03$] and younger ($r=-.28$, $P=.07$). There were no differences in depressive symptoms according to ethnicity, marital status, or educational background (Ps>.14). None of these demographic characteristics were associated with glucocorticoid sensitivity (Ps>.11), except for education, which had a positive relationship with the TNF-α IC_{50} ($r=.39$, $P=.02$). The correlations of depressive symptoms with IL-6 and TNF-α remained marginally significant after adjusting for demographic characteristics (Ps<.06).

Depressive symptoms were similar in patients with versus without histories of diabetes, hypertension, angina, myocardial infarction, congestive heart failure, ventricular arrhythmia, peripheral vascular disease, or cerebrovascular accident (Ps>.16). Medical history variables also were unrelated to glucocorticoid sensitivity for IL-1β, IL-6, and TNF-α (Ps>.11), except for diabetes; diabetic patients had higher IC_{50} values for IL-6 [$t(38)=2.10$, $P<.04$]. Adjustment for these conditions indicated that associations between depressive symptoms and IL-6 (Ps<.07) and TNF-α (Ps<.03) glucocorticoid sensitivity were independent of medical history.

Depressive symptoms were similar in patients who did versus did not have a history of coronary angioplasty, coronary bypass surgery, angiotensin receptor blockade, ACE inhibitors, antiarrythmics, anticoagulants, aspirin, beta-blockers, calcium-channel blockers, digitalis, diuretics, nitrates, statins, or vasodilators (all Ps>.19). Not surprisingly, patients who were taking antidepressants reported more severe depressive symptoms [$t(37)=2.19$, $P<.04$] than did those who were not. None of these medications or procedures were related to IC_{50} values for IL-6 or TNF-α (Ps<.12), and when we adjusted for them, there was very little change in the magnitude of the relationships between depressive symptoms and glucocorticoid sensitivity (for IL-6, Ps<.10; for TNF-α, Ps<.05).

Collectively, these findings indicate that demographic characteristics, medical status, and treatment regimens account for little, if any, of the observed correlations between depressive symptoms and enhanced IL-6 and TNF-α glucocorticoid sensitivity.

Discussion

Despite mounting evidence that depression increases the risk of cardiac morbidity and mortality, the biological mechanisms underlying this phenomenon are poorly understood [7,10]. The present study investigated whether depressive symptoms are associated with dysregulation of the immune response. Our findings suggest that in patients who are recovering from an acute coronary syndrome, depressive symptoms do not influence the capacity to mount an in vitro inflammatory cytokine response to infectious challenge. However, once this cytokine response has been activated by a pathogen, depressive symptoms are associated with a tendency towards overregulation, as shown by inverse relations between depressive symptoms and IC_{50} values for the cytokines IL-6 and TNF-α. Smaller concentrations of dexamethasone were required to suppress the in vitro production of these cytokines in samples drawn from patients with higher levels of depression.

How might enhanced IL-6 and TNF-α glucocorticoid sensitivity help to explain the excess morbidity and mortality among depressed cardiac patients? To clear invading pathogens from the body, the immune system must not only produce cytokines but also terminate this response at the correct time. To the extent that patients' white blood cells are overly sensitive to glucocorticoids, they may down-regulate the inflammatory response pre-

[1] An identical pattern of findings emerged when these analyses were reconducted treating baseline cytokine production as a covariate (for interleukin-6, $P<.04$; for tumor necrosis factor-α, $P=.03$; for interleukin-1β, $P=.31$). These findings indicate that baseline cytokine production is not acting as a confounder here, i.e., that depressed patients exhibit greater sensitivity to glucocorticoids, independent of how much inflammatory cytokine they produce in response to endotoxin challenge.

maturely, or do so in ways that compromise the immune system's ability to resist infection. This chain of events could facilitate the replication of invading pathogens and, by doing so, permit chronic and latent infections to be established within bodily tissues. Consistent with this line of reasoning, the prevalence of cytomegalovirus, chlamydia pneumoniae, and herpes simplex infections is markedly increased among cardiac patients who manifest depressive symptoms [8,16]. Although the evidence linking single infectious organisms to disease progression is mixed [24,25], there is consistent evidence of associations between pathogen burden (i.e., infection with multiple organisms) and cardiac endpoints [26–28].

If patients with depressive symptoms have *enhanced* sensitivity to the anti-inflammatory properties of glucocorticoids, why do they consistently exhibit increased circulating concentrations of inflammatory molecules such as CRP, IL-1β, and TNF-α [8]? It is possible that depressive symptoms might foster some processes that activate the inflammatory response. A number of stimuli could serve this function, including chronic infection, oxidative damage, weight gain, and vascular injury [29]. If depression does promote stimuli of this nature, the expression of inflammatory molecules could be sustained even in the context of enhanced glucocorticoid sensitivity. Regardless of how these findings are interpreted, the fact that depressed patients show evidence of systemic inflammation in concert with pathogen burden merits further attention. Mounting evidence indicates that these processes operate synergistically to increase the risk of morbidity and mortality [30–32]. This clustering of risk factors may help to explain depressed CHD patients' tendency to have worse medical outcomes.

It may be difficult to reconcile these findings with previous research on the biology of depression. Depression is marked by diminished glucocorticoid sensitivity in the central nervous system; dexamethasone challenge often fails to adequately suppress the morning cortisol response [33,34]. Reduced glucocorticoid sensitivity has also been found in the lymphocytes of depressed patients, such that dexamethasone's capacity to suppress mitogen-stimulated proliferation is diminished [34–36]. However, these findings have emerged in depressed patients who are medically healthy, and until now, nothing has been known about whether they extend to those with comorbid medical illness. Given the immunologic alterations that accompany advanced cardiac disease, it may be overly simplistic to assume that a similar pattern of findings will emerge in a sample like ours. It also bears noting that diminished glucocorticoid sensitivity is generally observed among severely impaired patients who are hospitalized. However, among patients with milder depressive symptoms, HPA axis function tends to be within normal limits, and in some cases, the output of cortisol is reduced [20,37–40]. If HPA output is blunted in cardiac patient populations in which depressive symptoms are quite mild, enhanced glucocorticoid sensitivity could be serving as a compensatory mechanism.

Unfortunately, indicators of cortisol output were not collected in this project, thus, we cannot evaluate the validity of this hypothesis. Future research that includes a comprehensive assessment of cortisol secretion patterns would greatly facilitate interpretation of these data.

This study has several limitations. The small number of patients who were involved and their narrow range of backgrounds limit the generalizability of the findings. The small sample size also reduced the statistical power to detect associations and precluded simultaneous adjustment for multiple confounders. The results would have been more compelling if cortisol, rather than dexamethasone, had been used to suppress cytokine production during infectious challenge. Although both of these molecules have potent anti-inflammatory properties, their differing patterns of interaction with glucocorticoid receptors and transcription factors raises questions about generalizability to in vivo circumstances. The cross-sectional design of the study limits any causal inferences that might be derived from the findings. We were able to rule out several competing explanations for the relationship between depressive symptoms and enhanced glucocorticoid sensitivity. For instance, disparities in the nature, severity, and treatment of patients' cardiac disease were not responsible for this association. However, given mounting evidence that exposure to inflammatory products can trigger behavioral disturbances that resemble symptoms of depression, the direction of the observed association remains unclear [41,42]. Depressive symptoms could be influencing immune regulation, immune regulation could be influencing depressive symptoms, or these processes could be reciprocal. Regardless of the initial causal trigger, however, the end result is increased vulnerability to adverse cardiac outcomes. In showing that depressive symptoms are associated with enhanced sensitivity to glucocorticoids, the present research may shed light on a basic immunological dysfunction that contributes to this phenomenon.

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