Increased Stress-Induced Inflammatory Responses in Male Patients With Major Depression and Increased Early Life Stress

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Objective: The authors sought to determine innate immune system activation following psychosocial stress in patients with major depression and increased early life stress.

Method: Plasma interleukin (IL)-6, lymphocyte subsets, and DNA binding of nuclear factor (NF)-κB in peripheral blood mononuclear cells were compared in medically healthy male subjects with current major depression and increased early life stress (N=14) versus nondepressed male comparison subjects (N=14) before and after completion of the Trier Social Stress Test.

Results: Trier Social Stress Test-induced increases in IL-6 and NF-κB DNA-binding were greater in major depression patients with increased early life stress and independently correlated with depression severity, but not early life stress. Natural killer (NK) cell percentages also increased following stress. However, there were no differences between groups and no correlation between NK cell percentage and stress-induced NF-κB DNA-binding or IL-6.

Conclusions: Male major depression patients with increased early life stress exhibit enhanced inflammatory responsiveness to psychosocial stress, providing preliminary indication of a link between major depression, early life stress and adverse health outcomes in diseases associated with inflammation.

Significant life stress, including early life stress, represents a major risk factor for development of major depression (1). Once manifested, major depression has been associated with increased tonic activation of the innate immune system, including increased plasma proinflammatory cytokines such as interleukin (IL)-6 (2). In nondepressed individuals, exposure to psychosocial stress has been associated with increased plasma IL-6 responses (3), as well as activation of nuclear factor (NF)-κB (4), a transcription factor that serves as a lynchpin in the inflammatory signaling cascade. Whether stress-induced increases in inflammatory activity are exaggerated in patients with psychiatric disease has not been examined. Given the relationship between early life stress and depression and the fact that psychosocial stress activates innate immune responses, we hypothesized that patients with major depression and increased early life stress would exhibit enhanced responsiveness of plasma IL-6 and NF-κB to psychosocial challenge.

Method

Twenty-eight male subjects, medically healthy as determined by physical examination and laboratory testing, were recruited between May 2003 and April 2005 as part of a study investigating the neurobiology of early life stress and major depression. Fourteen patients had current major depression, determined by Structured Clinical Interview for DSM-IV (SCID) (mean age=29.9 years). Twenty-one patients had current major depression, determined by Stru-
Lymphocyte subsets within isolated PBMCs (1×10⁶ cells obtained concurrently with NF-κB measures) were enumerated using fluorochrome-conjugated antibodies (BD Biosciences, Franklin Lakes, N.J.) directed toward CD16/56 (NK cells), CD4 (class II major histocompatibility complex [MHC] T cells), CD8 (class I MHC T cells), and CD20 (B cells) in a subset of depressed patients (n=7) and comparison subjects (n=10). Cells were analyzed using a FACScan flow cytometer (Beckham Coulter, Fullerton, Calif.) and FlowJo software.

Plasma IL-6 concentrations were compared between groups using 2-way ANOVA for repeated measures (time x group), with Huynh-Feldt adjustment for unequal variance. Differences from baseline were compared between groups by Mann-Whitney-U test. Independent sample t tests were used for between-group comparisons of baseline NF-κB activation and change in NF-κB DNA-binding and NK cell percentage from baseline to 30 minutes after Trier Social Stress Test onset (ΔIL-6) were compared between groups by Mann-Whitney-U test. Independent sample t tests were used for between-group comparisons of baseline NF-κB activation and change in NF-κB DNA-binding and NK cell percentage from baseline to 30 minutes after Trier Social Stress Test onset (ΔIL-6) were compared between groups by Mann-Whitney-U test. Independent sample t tests were used for between-group comparisons of baseline NF-κB activation and change in NF-κB DNA-binding and NK cell percentage from baseline to 30 minutes after Trier Social Stress Test onset (ΔIL-6) were compared between groups by Mann-Whitney-U test. Independent sample t tests were used for between-group comparisons of baseline NF-κB activation and change in NF-κB DNA-binding and NK cell percentage from baseline to 30 minutes after Trier Social Stress Test onset (ΔIL-6) were compared between groups by Mann-Whitney-U test. Independent sample t tests were used for between-group comparisons of baseline NF-κB activation and change in NF-κB DNA-binding and NK cell percentage from baseline to 30 minutes after Trier Social Stress Test onset (ΔIL-6) were compared between groups by Mann-Whitney-U test. Independent sample t tests were used for between-group comparisons of baseline NF-κB activation and change in NF-κB DNA-binding and NK cell percentage from baseline to 30 minutes after Trier Social Stress Test onset (ΔIL-6) were compared between groups by Mann-Whitney-U test. Independent sample t tests were used for between-group comparisons of baseline NF-κB activation and change in NF-κB DNA-binding and NK cell percentage from baseline to 30 minutes after Trier Social Stress Test onset (ΔIL-6) were compared between groups by Mann-Whitney-U test. Independent sample t tests were used for between-group comparisons of baseline NF-κB activation and change in NF-κB DNA-binding and NK cell percentage from baseline to 30 minutes after Trier Social Stress Test onset (ΔIL-6) were compared between groups by Mann-Whitney-U test. Independent sample t tests were used for between-group comparisons of baseline NF-κB activation and change in NF-κB DNA-binding and NK cell percentage from baseline to 30 minutes after Trier Social Stress Test onset (ΔIL-6) were compared between groups by Mann-Whitney-U test. Independent sample t tests were used for between-group comparisons of baseline NF-κB activat

Results

All participants displayed an increase in plasma IL-6 concentrations during Trier Social Stress Test challenge over time (F=10.32, df=1.92, P<0.001). There was also a significant interaction between sampling time and group (F=3.29, df=1.92, P<0.05). Post-hoc analysis (Bonferroni corrected for multiple comparisons) indicated that both groups had greater plasma IL-6 concentrations at 60, 75, and 90 minutes after Trier Social Stress Test onset relative to baseline. Depressed patients had higher IL-6 concentrations than comparison subjects at baseline and 90 minutes poststressor (Figure 1). Depressed patients also displayed a greater IL-6 response (ΔIL-6) to the Trier Social Stress Test than comparison subjects (Mann-Whitney U=44, P<0.05).

Baseline NF-κB DNA-binding (p65) did not differ between comparison subjects (4.8 ng [SD=2.5]) and depressed patients (5.2 ng [SD=2.5]). However, ΔNF-κB was greater in depressed patients (t=2.10, df=19, P<0.05) (Figure 1).

Hamilton depression scale scores were significantly correlated with ΔIL-6 (r=0.44, N=27, P=0.02) and ΔNF-κB (r=0.46, N=21, P<0.04). No significant correlations were observed between ΔIL-6 and ΔNF-κB or between Childhood Trauma Questionnaire scores and inflammatory measures. Multiple regression analyses indicated that Hamilton depression scale score was a significant independent predictor of ΔIL-6 (r²=0.42, P<0.04) and ΔNF-κB (r²=0.45, P<0.05, respectively), whereas partial correlation coefficients between Childhood Trauma Questionnaire score and immune variables (when controlling for Hamilton depression scale score) were not significant.

Among the lymphocyte subsets, only NK cell percentage significantly increased in response to Trier Social Stress Test in both groups. However, ΔNK did not differ between major depression patients (15.1% [SD=7.9]) and comparison subjects (14.8% [SD=8.6]). Moreover, ΔNF-κB and ΔNK were not correlated (r=0.015, N=14, P=0.96), nor was ΔNK correlated with ΔIL-6 (r=0.050, N=16, P=0.85) or Hamilton depression scale score (r=0.28, N=17, P=0.27). In addition,
ΔNF-kB was not correlated with Trier Social Stress Test-induced changes in other PBMC subsets (data not shown).

Discussion

Although previous studies have shown evidence of increased baseline activation of the inflammatory response in major depression patients (e.g., 2), the current study extends these findings by providing the first evidence that the inflammatory response to stress is exaggerated in major depression patients, specifically male patients with major depression and increased early life stress. This difference was observable only at later timepoints following Trier Social Stress Test onset, and may explain why previous studies have failed to identify increased inflammatory responses after psychological stress (6). Interestingly, baseline elevations in plasma IL-6 concentrations in major depression patients with increased early life stress were similar to maximal stress-induced IL-6 responses in comparison subjects, suggesting that male major depression patients with increased early life stress may chronically exhibit stressed-induced increases in inflammatory markers that are further exacerbated by exposure to acute stress. These findings indicate that depressed patients with increased early life stress exhibit both a baseline hyperinflammatory state coupled with a hyper-responsive inflammatory response to stress, which together may contribute to medical comorbidities associated with major depression and inflammation such as cardiovascular disease (7).

Previous work suggests that stress-induced changes in NF-kB DNA binding may result from shifts in lymphocyte subpopulations during exercise stress (8). In particular, NK cells have been shown to exhibit high constitutive levels of NF-kB DNA binding, and NK cell percentage increases following stress. While NK cell percentages did increase as a result of the Trier Social Stress Test, the magnitude of this increase did not differ between groups, nor did it correlate with stress-induced changes in NF-kB or IL-6. The lack of a relationship between NK cells and IL-6 is consistent with a recent report (9). However, dissociation between NF-kB and NK cell percentage in this and previous studies may be a function of the stressors employed (public speaking/mental arithmetic), which qualitatively differ from exercise.

Of particular importance is that major depression patients in this study had significantly higher Childhood Trauma Questionnaire scores (early life stress) than comparison subjects. As previously reported, early life stress is commonly associated with major depression (10) and has been associated with distinct neurobiological responses to stress (11). Indeed, previous stressor exposure has been shown to sensitize subsequent immune responses to immune challenge (12), and therefore the findings may result from an interaction between major depression and early life stress. Nevertheless, depression scores exhibited a significant independent relationship with immune variables, whereas Childhood Trauma Questionnaire scores did not. However, due to the relatively small study group size and study design, the relative contribution of early life stress alone or in combination with major depression cannot be definitively established. Correlation coefficients observed between Childhood Trauma Questionnaire scores and inflammatory markers represented small-to-medium effect sizes that would require total sample sizes of N≥70 to have sufficient power (80%) to detect significance using a two-sided test (p≤0.05) (13). These potential relationships would be best revealed in future studies using a stratified design with a larger sample size.

The mechanisms of the observed effects may relate to changes in neuroendocrine function, including increased sympathetic nervous system responses and/or altered glucocorticoid feedback regulation. Sympathetic nervous system activation has been shown to enhance inflammatory responses (4), and major depression patients with early life stress have been shown to exhibit enhanced sympathetic nervous system responses to stressor challenge (11). In addition, alterations in glucocorticoid feedback, which play an important role in modulating inflammatory responses, have been described in major depression patients (14). Taken together, the data suggest that further studies examining the independent contributions of major depression and early life stress to the inflammatory response to stress as well as the mechanisms involved are warranted.

Presented in part at the 12th annual meeting of the Psychoneuroimmunology Research Society, Denver, June 9–11, 2005. Received March 3, 2006; revision received May 1, 2006; accepted May 11, 2006. From the Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine. Address correspondence and reprint requests to Dr. Miller, Emory University School of Medicine, WMRB Suite 4000, Atlanta, GA 30322.

Dr. Nemeroff reports grants/research funding from the American Foundation for Suicide Prevention (AFSP), AstraZeneca, Bristol Myers Squibb, Cyberonics, Forest Laboratories, Janssen Pharmaceutica, NARSAD, NIMH, Pfizer, and Wyeth-Ayerst. He has been a consultant for Abbott Laboratories, Acadia Pharmaceuticals, Bristol Myers Squibb, Corcept, Cypress Biosciences, Cyberonics, Eli Lilly, Entrepeneur’s Fund, Forest Laboratories, GlaxoSmithKline, I3 DLN, Janssen Pharmaceutica, Lundbeck, Otsuka, Pfizer, Quintiles, UCB Pharma, and Wyeth-Ayerst. He has participated in the Speaker’s Bureau for Abbott Laboratories, GlaxoSmithKline, Janssen Pharmaceutica, and Pfizer. He is a stockholder in Acadia Pharmaceuticals, Corcept, Cypress Biosciences, and NovaDel. He serves on the Board of Directors for AFSP; American Psychiatric Institute for Research and Education (APIRE); George West Mental Health Foundation, NovaDel Pharma, and the National Foundation for Mental Health. He holds patents for method and devices for transdermal delivery of lithium (U.S. 6,375,990 B1) and the method to estimate serotonin and norepinephrine transporter occupancy after drug treatment using patient or animal serum (provisional filing, April 2001). He reports equity in Reevaax, BCMJR LLC, and CeNeRx.

This work was supported by PHS grants NCRR M01-RR00039 (Emory University Hospital General Clinical Research Center), MH-58299 (The Emory Conte Center for the Psychobiology of Early Life Trauma), HL-065523 (to Dr. Musselman), and a 2002 NARSAD Young Investigator Award (to Dr. Heim).
Further Evidence for a Developmental Subtype of Bipolar Disorder Defined by Age at Onset: Results From the National Epidemiologic Survey on Alcohol and Related Conditions

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Objective: This study examines the relationship between age at onset of bipolar I disorder and illness characteristics among adults in a community sample.

Method: The National Epidemiologic Survey on Alcohol and Related Conditions identified 1,411 adults with bipolar disorder. For analyses, bipolar disorder subjects were divided into three age at onset groups: childhood (less than 13 years old, N=113), adolescence (13–18 years old, N=339), and adulthood (19 years or older, N=959).

Results: Nonremitting bipolar disorder was most prevalent among childhood-onset subjects, and childhood-onset subjects were most likely to experience prolonged episodes. Antisocial personality disorder was most prevalent among childhood-onset subjects. Drug use disorders were more prevalent among childhood-onset and adolescent-onset, as compared with adult-onset, subjects. Prevalence of mixed episodes or irritability did not differ significantly between groups.

Conclusions: Findings corroborate clinical studies: illness characteristics among adults with childhood-onset bipolar disorder are similar to those described in children with bipolar disorder.

Recent studies suggest that a developmental subtype of bipolar disorder can be identified by age at onset of bipolar disorder (1, 2). Adults with juvenile-onset bipolar disorder report chronic and unremitting illness, predominance of irritability as compared to euphoria, and mixed mania. These features are similar to illness characteristics described in prospective evaluations of children with bipolar disorder. Furthermore, oppositional defiant disorder/conduct disorder is one of the most common comorbid conditions of childhood bipolar disorder (3, 4), and