Acute Psychological Stress: Effects on Chemotaxis and Cellular Adhesion Molecule Expression

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Objective: Activation of a psychological stress response increases autonomic activity and enhances immune function by inducing a significant increase in numbers of leukocytes at sites of inflammation. Chemotaxis and cellular adhesion are thought to mediate leukocyte trafficking. In this study, we examine the effects of an acute psychological stress on chemotactic responses of PBMCs and on CAM expression in relation to measures of sympathetic activation. **Methods:** Subjects underwent either a public speaking task ($N = 24$) or a control condition ($N = 13$). Blood was drawn before the task, immediately after, and 20 minutes after, the task for changes in percentage of cells expressing cellular adhesion molecules, chemotaxis to chemokines, HR, blood pressure, and E and NE levels. **Results:** In response to the laboratory stressor, increases of PBMC chemotaxis to FMLP and SDF-1 were found, which were coupled with increases in the percentages of lymphocytes expressing the integrin Mac-1. Autonomic activity, including blood pressure and circulating levels of catecholamines, increased after administration of the stressor, and correlated with increases of Mac-1. **Conclusions:** These data show that acute stress induces increase of chemotaxis and expression of CAM expression, which may contribute to increased migration and recruitment of immune cells to sites of infection and/or inflammation. **Key words:** chemotaxis, immunity, cellular adhesion molecule, psychological stress, sympathetic nervous system.

PBMC = peripheral blood mononuclear cell; **E** = epinephrine; **NE** = norepinephrine; **CAM** = cellular adhesion molecule; **Mac** = macrophage-associated antigen; **LFA** = lymphocyte functional antigen; **SDF** = stromal-cell derived factor; **FMLP** = *f-met-leu-phe*; **RANTES** = regulated on activation normal T expressed and secreted chemokine; **IL** = interleukin; **MCP** = monocyte chemoattractant peptide; **ICAM** = intercellular adhesion molecule; **SCID** = Structured Clinical Interview for DSM-IV; **DSM** = Diagnostic and Statistical Manual; **PBS** = phosphate-buffered saline; **PE** = phycoerythrin; **FITC** = fluorescein isothiocyanate; **HR** = heart rate; **SBP** = systolic blood pressure; **DBP** = diastolic blood pressure; **ANOVA** = analysis of variance; **DTH** = delayed type hypersensitivity.

INTRODUCTION

Acute stress results in a redistribution of leukocytes from the blood to other organs in the body, and has been found to increase immune function in animals. This rapid redeployment of immune cells out of the blood is thought be due to increases of chemotaxis and of CAM expression (1, 2) two components critical in the recruitment and migration of immune cells to sites of inflammation. However, translation of these basic observations is limited. Prior studies in humans have not examined the effects of stress on chemotaxis and few studies have evaluated the association between stress and CAM expression. It is known, however, that psychological stress induces increases of immunoregulatory cell number and function via adrenergic receptor activation in humans (3–7).

Chemokines provide specific signaling to leukocytes for extravasation from the blood, and direct locomotion and microenvironmental homing of leukocytes within tissues (8), all of which are critical for the accumulation of immune cells at sites of infection. In addition, CAM expression of L-selectin leads to preferential cell recruitment by enhancing binding to locally expressed ligands. With subsequent immune activation, L-selectin is cleaved (9), and integrins such as Mac-1 and LFA-1 transition into the active state (10), which lead to firm adhesion and transendothelial migration via interaction with endothelial counterligands, such as ICAM-1. In humans, there is some evidence that psychological stress alters cellular expression of adhesion molecules on leukocytes with increases in the density of LFA-1 on mixed lymphocytes (11, 12).

Given the important role of immune cell recruitment and migration in inflammation and role of stress in mediating leukocyte trafficking, this study examined the effects of psychological stress on chemotaxis and CAM expression. Responses to five chemokines (FMLP, SDF-1, RANTES, IL-8, and MCP-1) were measured along with measurement of the percentage of lymphocytes expressing L-selectin and Mac-1 and assay of circulating concentrations of L-selectin. We hypothesize that stress will enhance chemotaxis and leukocyte CAM expression, and that activation of the sympathetic nervous system will be related to the immunological effects of psychological stress.

METHODS

Subjects

Subjects included ($N = 37$) healthy African-American volunteers (17 men and 20 women) ranging in age from 25 to 50 years with a mean age of 35. Subjects were recruited from advertisements in local newspapers. An initial phone screening was conducted before entry into the study. Causes for exclusion included current moderate to severe depressive symptoms or diagnosis of current major depression, current alcohol abuse, and use of any prescriptive or over-the-counter medications, except for analgesic use, up to 24 hours before the session and no analgesics within 24 hours of the study session. Psychiatric diagnoses of exclusion were established after administration of the mood and drug and alcohol sections of the SCID. In addition, a detailed medical history was obtained. Of the 40 individuals who gave informed consent, 3 individual failed to meet eligibility criteria and were excluded. Eligible subjects ($N = 37$) were randomly assigned at a 2:1 ratio into one of two conditions, a public speaking ($N = 24$) task or a no-stress control ($N = 13$) task where subjects read magazines.

Procedures

Experimental Overview

Subjects arrived between 8:30 and 9:30 AM, signed a consent form, and were then evaluated for psychiatric and medical illnesses. Subjects were seated in a semirecumbent position and instructed not to watch while an

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intravenous catheter was inserted into a superficial vein of the nondominant forearm. A blood pressure cuff was placed on the dominant arm and was connected to a Dinamap machine for automatic measurements of HR and systolic and diastolic blood pressure throughout the session. Before a baseline blood draw, subjects rested for 45 minutes. For the first 30 minutes subjects filled out questionnaires and read magazines. During the last 15 minutes of the rest period, the subjects remained unoccupied and HR and blood pressure were taken three consecutive times during the last 5 minutes of the rest period. A baseline blood draw (30 ml) was taken immediately after for immune measures. Next, the second HR and blood pressures were measured three consecutive times over the five minutes during the speech and blood draws were taken immediately afterward (+0). Final HR and blood pressures were measured three consecutive times (+15 minutes) after the task and blood was drawn 20 minutes after the task (time +20). Autonomic measures were taken immediately before blood draws instead of during blood draws to reduce the distress effects of having blood taken on autonomic measures. In total, there were three blood draws and three sets of autonomic measures during each session.

Tasks

A well-documented standardized speech protocol, which has been used for both African-American and white subjects for the evaluation of neuroendocrine/sympathetic nervous system stress responsivity, eg (11), was utilized for the present investigation. Briefly, subjects in the stress group were instructed to prepare for 5 minutes and give a speech for an additional 5 minutes pertaining to a scenario of being fired on the grounds of inadequate productivity due to an unreliable associate. Subjects remained seated during the speech task and they were told that the speech would be evaluated on the use of grammar, vocabulary, and body language. A member of the research staff videotaped and timed the speech and reminded subjects to continue speaking if they stopped before the time was up. The control group was instructed to read a magazine for 10 minutes in lieu of the speech task.

Chemotaxis of Peripheral Blood Mononuclear Cells

Twenty milliliters of blood were collected into heparinized tubes for each time point and processed immediately after the session. PBMCs were separated from whole blood with the use of Ficoll-Hypaque sedimentation and resuspended in RPMI 1640 with 20 mM HEPES (serum-free media). Cells were incubated for 45 minutes at room temperature in the dark, and were shaken lightly with 0.1 uM calcein-AM (acetoxymethyl ester)/2 $\times$ 10^6 cells/ml serum free media see (13). Cells were then washed and resuspended to 3 $\times$ 10^6 cell/ml RPMI 1640 with 20 mM HEPES, L-glutamine, and 0.1% bovine serum albumin (chemotaxis buffer). In a modified Boyden chamber (Neuroprobe, Gaithersburg, MD), 29.5 μl of chemokines or chemotaxis buffer were pipetted into each well at the bottom of the chamber. Because human studies examining psychological stress and chemotaxis to chemokines had not been performed previously, a variety of chemokines were chosen from different categories (immune cell subsets and chemokine receptor type) to explore their potencies in relation to the stress task. Chemoattractants for B-cells, T-cells and monocytes were chosen as well as one general chemoattractant, to examine the role of various immune cell responses to chemokines in reaction to stress. Chemokines are a superfamily of small structurally related chemotactic cytokines. The CC chemokine is the largest class, where the first two cysteines are adjacent, whereas CXC is the second largest class and the first two cysteines are separated by an amino acid residue (14). RANTES (binds to CCR1 and CCR5 receptors) and MCP-1 (binds to CCR2 receptors) are thought to preferably attract T vs. B cells (15) (16), although CCR5 receptors are also present on B-cells (17). IL-8 (binds to CXCL-8 receptors) primarily attracts B cells (18) and not T cells (16) or monocytes (15). SDF-1 (binds to CXCR4 receptors) also strongly attracts B cells, but also attracts monocytes (19) and CXCR4 receptors are present on T cells (17). FMLP is a bacterial peptide that is a general chemoattractant and attracts various immune cells (1). Chemokines were used at an optimal dose that was determined after a series of pilot studies, and the following chemokine concentrations were used: 50 ng/ml RANTES, 50 ng/ml SDF-1, 50 ng/ml MCP-1, and 25 ng/ml IL-8 (Biosource, Camarillo, CA), and 10 nM FMLP (Sigma). After the pipetting of chemokines, the membrane was snapped on top of the plate and 20 μl of cell suspension was added to the top of each well. Cells were incubated for 2 hours at 37°C and then the top of the membrane was gently rinsed with PBS and nonmigrated cells were scraped away with the use of PBS-dampened cotton swabs. The membrane was removed from the plate and briefly submerged in PBS. Once dry, the membrane was read by a fluorescence plate reader (CytoFluor) at an excitation of 485 nm and emission of 530 nm.

Cellular and Soluble Adhesion Molecule Measures

Whole blood was collected into heparinized tubes at the three time points and assayed within 3 hours of collection. Flow cytometry (FACScan, Becton-Dickinson, San Jose, CA) using SimulSET software was used with CD45 gating to quantify leukocytes and CAMs. To prepare leukocytes, aliquots of whole blood (490 μl) from each time point were stimulated for 30 minutes at room temperature with 10 μl of 10^{-5} FMLP diluted in serum-free RPMI. The reaction was stopped with 10 ml of cold PBS and the blood was centrifuged for 10 minutes at 1,200 rpm. Most of the supernatant was removed, leaving 800 μl of PBS/pellet that was separated into four tubes of 200 μl each. The samples were incubated at room temperature for 15 minutes with PE-conjugated monoclonal antibodies for L-selectin (CD62L) and Mac-1 (CD11b), and FITC for CD45 (Becton-Dickinson). An isotypic control (IgG-PE), was used for each assay to determine nonspecific staining. After incubation, the red blood cells were lysed with FACSLyse solution (Becton-Dickinson), followed by washing with 2 ml of PBS, centrifugation for 10 minutes at 1,200 rpm and aspiration of the supernatant. Labeled cells were fixed with 2% formaldehyde in PBS and analyzed by flow cytometry within 24 hours. Quantikine human soluble L-selectin (R&D Systems, Minneapolis, MN) kits were used.

NE and E Measures

Blood samples for catecholamines were collected on ice and separated in a refrigerated centrifuge, and plasma was stored at −80°C until assay. NE and E were determined by radioenzymatic assay (20). The intra- and interassay coefficients of variation for the assay are 6.5% and 11%, respectively.

Statistical Analyses

To evaluate changes in autonomic, catecholamine, and percent positive leukocytes for CAMs, concentrations of soluble CAMs and PBMC migration to chemokines, a 2 (groups = speech task, reading task) $\times$ 3 (time points = BL, +0, +20) repeated-measures ANOVA was used. In addition, partial correlations were used to examine relationships between catecholamines and recruitment/migration variables, ie, CAMs and PBMC chemotaxis, postspeech, or reading task. Basal levels were used as covariates.

RESULTS

The two groups were not significantly different in age, with a mean age of 34.1 years in the stress group and 37.7 years in the no-stress control condition. There were no significant differences between groups in gender distribution.

HR and Blood Pressure

There was a significant group $\times$ time ($F = 7.1$, $p = .002$) interaction for HR with an increase in HR during the task in the stress group. For SBP there was a group $\times$ time interaction ($F = 6.24$, $p = .004$), with increases in SBP response to the stress task. DBP increased in the stress group in response to the task and there was a group $\times$ time interaction ($F = 15.6$, $p < .001$) in DBP. The data for HR and blood pressure are presented in Table 1.

NE and E

In order to normalize the data for NE and E, the log was derived for repeated-measures ANOVA analyses. For E, but

TABLE 1. Heart Rate, Blood Pressure and Catecholamine Levels Across the Session

	Stress (mean ± SD)			No Stress (mean ± SD)		
	Baseline	+0	+20	Baseline	+0	+20
Heart rate (bpm)[a]	66.3 (1.1)	73.8 (9.3)	66.0 (8.6)	61.9 (11.2)	61.1 (10.8)	61.4 (11.0)
Systolic blood Pressure (mm Hg)[a]	122.4 (6.8)	129.4 (10.3)	121.4 (9.7)	118.2 (10.2)	119.5 (9.6)	120.6 (9.2)
Diastolic blood Pressure (mm Hg)[a]	66.8 (8.4)	73.8 (11.0)	63.4 (9.8)	68.2 (10.5)	66.9 (10.6)	68.8 (9.8)
Norepinephrine (LN, pg/ml)	5.5 (.41)	5.7 (.42)	5.6 (.36)	5.5 (.30)	5.5 (.33)	5.5 (.37)
Epinepherine (LN, pg/ml)[a]	2.5 (.79)	2.8 (.79)	2.5 (.84)	2.7 (.68)	2.7 (.71)	2.8 (.56)

[a] Significant group × time interaction ($p < .05$).

not NE, there was a group × time interaction ($F = 3.2$, $p = .05$), in which E levels increased in response to the stress task.

Immune Measures

Chemotaxis of Peripheral Blood Lymphocytes

For chemotaxis to 10 nM FMLP, there was a significant group × time interaction ($F = 3.7$, $p = .03$), showing an increase in chemotaxis to FMLP in response to the speech task (Figure 1). For chemotaxis to SDF-1 (Figure 2) there was a significant group × time interaction ($F = 3.2$, $p = .05$), also revealing an increase in chemotaxis in response to stress. For RANTES and IL-8 there were trends toward group × time interactions ($F = 1.95$, $p = .1$; $F = 3.0$, $p = .06$, respectively), but no effects for MCP-1.

CAMs

Percentages of lymphocytes positive for CAMs, Mac-1, and L-selectin were examined over the course of the session. For Mac-1 there was a group × time interaction ($F = 3.2$, $p = .05$), in which Mac-1 positive lymphocytes increased in response to the stress task (Figure 3). For L-selectin there was also a significant group × time interaction ($F = 6.1$, $p = .004$) with percentages of L-selectin positive lymphocytes decreas-

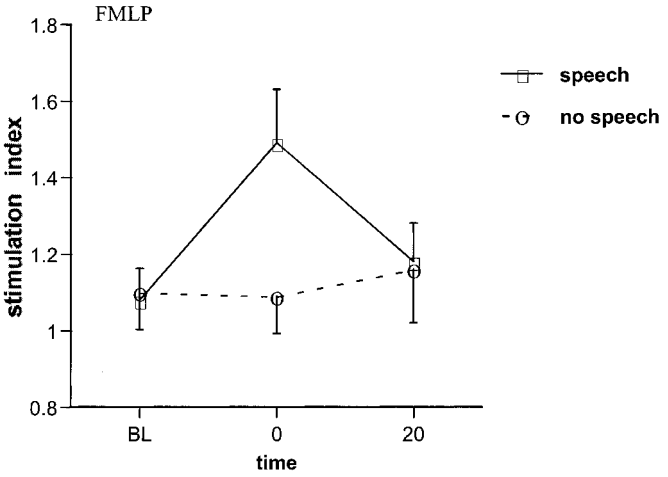

Fig. 1. Chemotaxis of peripheral blood mononuclear cells from African-American subjects reading magazines (*o*) or undergoing a speech task (127). Data are presented as cells migrating to FMLP-divided random migration of cells to media ± SEM. Blood was drawn at baseline (BL), immediately after the speech/reading task (0), and 20 minutes after the task (20). The two groups showed a differential change across the session with a significant group × time interaction ($F[2,54] = 3.7$, $p = .03$).

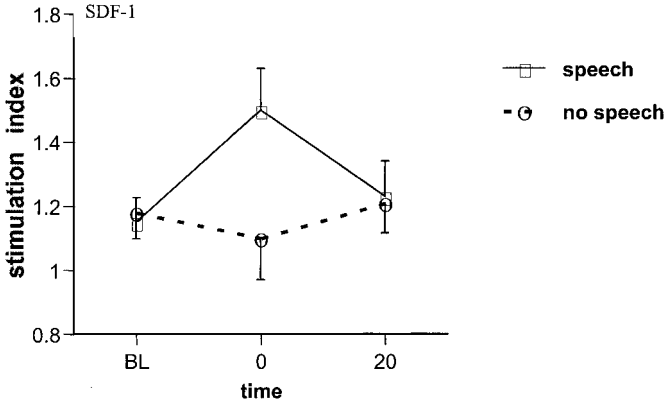

Fig. 2. Chemotaxis of peripheral blood mononuclear cells from African-American subjects reading magazines (*o*) or undergoing a speech task (127). Data are presented as cells migrating to SDF-1 divided random migration of cells to media ± SE. Blood was drawn at BL, immediately after the speech/reading task (0), and 20 minutes after the task (20). The two groups showed a differential change across the session with a significant group × time interaction ($F[2,54] = 3.2$, $p < .05$).

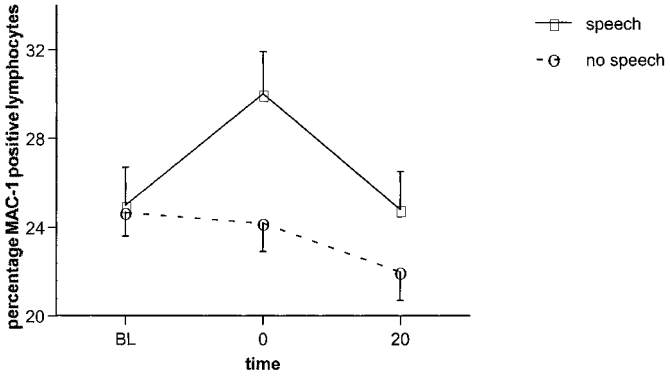

Fig. 3. Percentage of Mac-1 positive lymphocytes from African-American subjects reading magazines (*o*) or undergoing a speech task (127). Data are presented as mean ± SE. Blood was drawn at BL, immediately after the speech/reading task (0), and 20 minutes after the task (20). The two groups showed a differential change across the session with a significant group × time interaction ($F(2,54) = 3.2$, $p < .05$).

ing in response to the task (Figure 4). There were no significant group × time interactions for percentages of monocytes positive for Mac-1 and L-selectin. Partial correlations revealed that lymphocyte Mac-1 expression was negatively correlated with L-selectin after covarying for baseline Mac-1 and L-selectin levels ($r = -0.73$, $p < .01$), which suggests that the decrease in L-selectin is related to an increase in Mac-1 expression after stress.

Soluble L-Selectin

Levels of soluble L-selectin changed differentially in response to the speech stress as compared with the control condition (Figure 5). There was a significant group × time interaction ($F = 3.1$, $p = .05$) with increases in L-selectin in response to the stress task.

Relationships Between NE and E and Immune Measures, CAMs, and Chemotaxis

Partial correlations revealed that lymphocyte Mac-1 expression was positively correlated with E levels post task after covarying for basal E and Mac-1 levels (Figure 6). This suggests that increases in E are associated with increases in Mac-1 immediately after the task ($r = .43$, $p = .05$). Also, lymphocyte L-selectin expression was negatively correlated with E after the task (Figure 7), after covarying for basal E levels and L-selectin expression ($r = -0.46$, $p = .04$). However, there were no significant correlations with these CAMs and NE, or between measures of chemotaxis and E or NE.

DISCUSSION

Recruitment and migration of immune cells are vital in immunological responses; however, few human studies have examined the effects of stress on leukocyte motility and to our knowledge there are no published studies examining psychological stress and leukocyte chemotaxis. The present study measured chemotactic responses of peripheral blood mononuclear cells to an acute speech stressor. In addition, observations were extended from previous studies on the effects of acute stress on CAM expression by examining Mac-1 on leukocytes and soluble L-selectin levels in plasma. Peripheral blood mononuclear cell chemotaxis significantly increased to chemokines FMLP and SDF-1 and there were trends toward increased chemotaxis to RANTES and IL-8. Although not previously reported in humans, these results extend the findings of enhanced chemotaxis in response to swim stress in mice and guinea pigs (1) and increased DTH responses in rats in response to restraint (21).

In addition, the present study found that Mac-1 positive lymphocyte expression increased, and L-selectin expression decreased, which supported and extended previous findings. Acute psychological stress was found to increase another

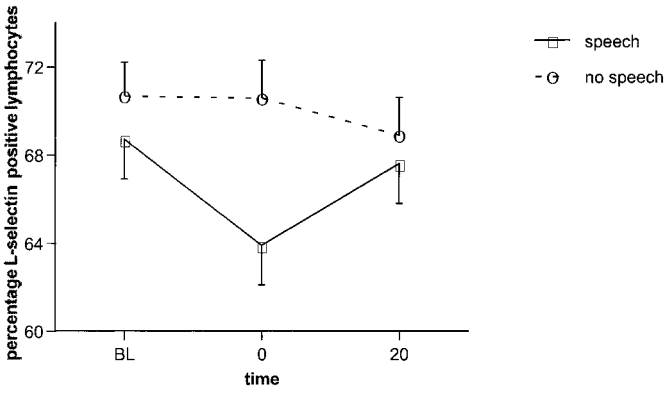

Fig. 4. Percentage of L-selectin positive lymphocytes from African-American subjects reading magazines (*o*) or undergoing a speech task (127). Data are presented as means ± SE. Blood was drawn at BL, immediately after the speech/reading task (0), and 20 minutes after the task (20). The two groups showed a differential change across the session with a significant group × time interaction ($F(2,54) = 6.1$, $p = .004$).

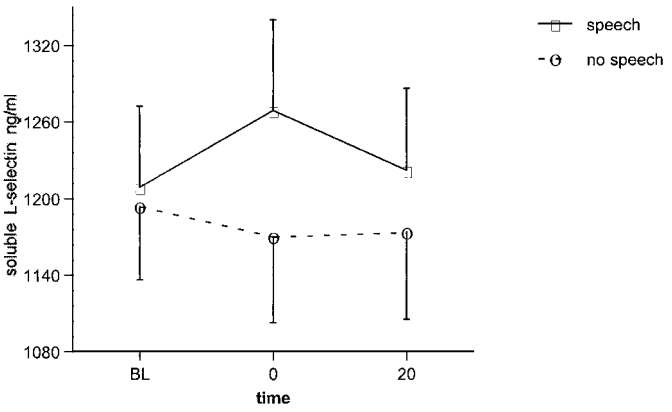

Fig. 5. Plasma levels of soluble L-selectin from African-American subjects reading magazines (*o*) or undergoing a speech task (□). Data are presented as mean (ng/ml) ± SE. Blood was drawn at BL, immediately after the speech/reading task (0), and 20 minutes after the task (20). The two groups showed a differential change across the session with a significant group × time interaction ($F(2,54) = 3.1$, $p = .05$).

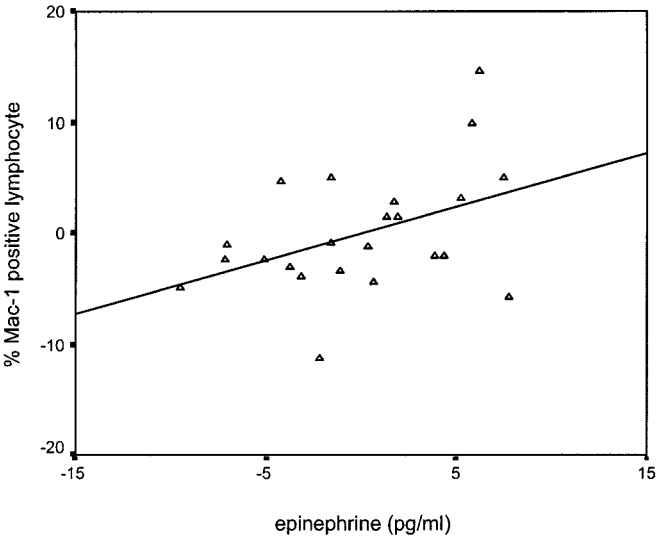

Fig. 6. A significant positive correlation between lymphocyte Mac-1 expression and E levels immediately after the task was revealed after covarying for basal Mac-1 and E levels ($r = .43$, $p = .05$).

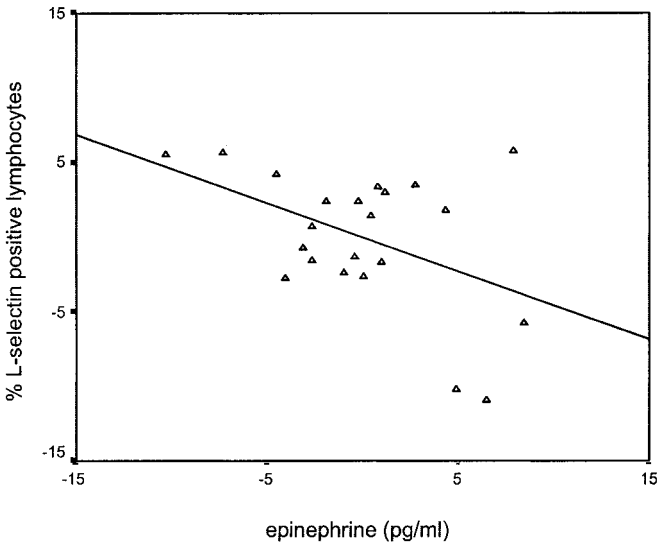

Fig. 7. A significant negative correlation between lymphocyte L-selectin expression and E levels immediately after the task was found after covarying for basal L-selectin and E levels ($r = -0.46$, $p = .04$).

integrin, LFA-1, and to decrease in L-selectin expression (11, 12). Along with reduced lymphocyte L-selectin expression in the present study, there was an increase in plasma levels of soluble L-selectin in response to stress, suggesting possible stress-induced shedding of L-selectin (9). Importantly, these changes of CAM expression may be driven by sympathetic activation. A relationship between catecholamines and adhesion molecule expression was found in which catecholamine levels were positively associated with Mac-1 and negatively associated with L-selectin expression on lymphocytes. This extends previous findings of isoproterenol injection-induced increases in integrin LFA-1 expression (22) and a propranolol-induced reduction of psychological stress-induced increases in the density of LFA-1 on lymphocytes (23). It also suggests that epinephrine may activate immune cells to shed L-selectin. However, in contrast to our hypothesis, chemotaxis was not correlated with catecholamine levels, suggesting that another mechanism of activation may also exist, which increases chemotaxis after stress. Corticosteroids have also been identified as hormonal mediators of stress-induced trafficking (21); however, we did not measure cortisol in the present study.

The present study examined immunological recruitment and migration factors, and similar to other immune measures previously examined, increased responses to acute stress were found. Increases in immunological responses, such as chemotaxis and CAM expression responses may represent allostasis, where, during acute responses, the human body's activity responds to a challenge to keep the organism in balance (24). However, with prolonged stress there may be deleterious consequences resulting from allostatic load, an imbalance in the physiological systems resulting in wear and tear on the body (24). Chronic stress-induced immune alterations may be important in cardiovascular disease such as atherosclerosis and clinical manifestations of atherosclerosis, such as myocardial infarction.

Atherosclerosis is thought to be mediated by immune components such as, chemokines, cytokines and CAMs, which are suggested to be involved in adherence and migration of immune cells into aortic intima (25). Chemokines, such as MCP-1, RANTES, IL-8, and MIP-1β have been identified in human atherosclerotic lesions (14, 26). SDF-α receptors are found to increase by three to four times on macrophage-derived foam cells on treatment with oxidized low-density lipoproteins (27). In addition, chemokines appear to interact with CAMs to increase immune cell adhesion to endothelium by stimulating a high affinity state in the integrin molecule (28). Once within the aortic intima, macrophages can engulf oxidized low-density lipoproteins, causing fatty streaks and atherogenic lesions (29).

The present study examined African Americans because substantial epidemiological evidence indicates that African Americans have increased morbidity with elevated risk for hypertensive cardiovascular disease, cancer, and infections as compared with whites (30). Although the mechanisms involved in the association between African-American ethnicity and disease are still not fully understood, psychosomatic models suggest that racial health differences, such as high rates of coronary heart disease, are produced from socio-environmental stress (31). Furthermore, stress-related alterations in physiological activity are thought to mediate these health consequences in the African-American population (32).

With the establishment that African Americans in the present study were responsive to the experimental manipulations, future studies should include comparisons between various racial and ethnic groups to determine whether findings in the present study in African Americans differs or is similar, both basally and in response to stress. Also, it would be important to follow subjects over time to determine whether racial and ethnic differences in immunological measures predict future disease outcome.

There were several limitations in the present study, which may be resolved in future studies, such as performing a dose response curve for chemokines at each time point. Although dose response curves generated before this research study suggested that the doses of chemokines used were optimal at rest, varying concentrations of chemokines may affect different subsets of leukocytes in response to a stressor. In addition, exploring sympathetic mediation using more sophisticated measures may be beneficial to understanding stress responsivity and immunological alterations. Looking at adrenergic receptor sensitivity and density on the immune cells may further establish relationships between catecholamines and immune changes to acute and prolonged stress. Also, looking at direct effects of addition of epinephrine in vitro with changes in expression of adhesion molecule expression and chemotaxis would strengthen the sympathetic immune recruitment and migration connection. In addition, the speech task vs. the reading task in the present study may have had uncontrolled differential elements that contribute to alterations found in physiological measures, beyond the psychological stress component (eg, increased arm movements while talk-

ing). However, prior research shows that the act of speaking in the speech task condition vs. the control condition does not contribute to the changes in immune, autonomic, or adrenergic-receptor activity (33).

In conclusion, acute stress induces increases in PBMC chemotaxis, Mac-1 expression on lymphocytes, and soluble plasma L-selectin levels in African Americans. These preliminary findings suggest that further study is necessary to determine whether increased cardiovascular disease risk in African Americans results from sympathetic and autonomic activity induced alterations in immune recruitment and migration factors. Interventions may be then developed to mitigate these disease processes.

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