Adrenergic Blockade Ameliorates Cellular Immune Responses to Mental Stress in Humans

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This study evaluated the sympathoadrenal modulation of behaviorally evoked immune responses by administration of a nonselective adrenoceptor antagonist (labetalol) to subjects exposed to mental stress. In a 2 × 2 factorial design, subjects were assigned to a labetalol or saline condition and, within each condition, were exposed either to acute laboratory stress or no stress (control). Lymphocyte subsets, natural killer (NK) cell cytotoxicity, and T cell proliferation to phytohemagglutinin and concanavalin A were assessed pre-experimentally, at baseline after infusion and after 18 minutes of mental stress (or rest). By comparison with the other three conditions, the saline-stress group showed a greater peripheral NK cell number and cytotoxicity, lower mitogenic response to phytohemagglutinin and concanavalin A, and diminished ratio of CD4:CD8 cells after the stressor. As predicted, immune responses did not differ among the remaining groups (labetalol-stress, saline-rest, labetalol-rest). Group differences in NK cell cytotoxicity were not significant after controlling for differences in NK cell numbers. These findings demonstrate that the occurrence of certain immunologic responses to acute psychological stress are dependent on concomitant activation of the sympathetic nervous system.

Key words: Psychoneuroimmunology, neuroimmunomodulation, cellular immune response, acute psychological stress, sympathetic nervous system

INTRODUCTION

There is now substantial evidence that aspects of cellular immune function may be altered after exposure to acute mental stress. The most consistent immunologic changes reported in these investigations include an increase in the number of circulating natural killer (NK) and T suppressor/cytotoxic (CD8) lymphocytes, a decrease in the ratio of T helper to T suppressor cells (CD4:CD8), reduced lymphocyte mitogenesis, and altered NK cell activity (1–6).

Although the mechanism(s) underlying acute immunologic reactions to stress remain unclear, there is indirect evidence that such changes may be mediated by concomitant sympathoadrenal activation. In this respect, it has been shown that: a) sympathetic nerve endings innervate lymphoid tissue (7); b) behavioral stimuli that evoke changes in cellular immunity similarly induce sympathetic arousal, as evidenced by acute rises in heart rate, blood pressure, and plasma catecholamine concentrations (1–3, 6); c) immune responses to acute mental stress (i.e., a selective increase in CD8 cells and decreased lymphocyte proliferation) covary with the magnitude of sympathetic activation elicited under the same stimulus conditions (2–3, 6); d) immunologic changes in such studies occur earlier than can be explained by activation of the pituitary-adrenocortical axis (e.g., within 5 minutes) and in the absence of a concomitant rise in plasma cortisol concentrations (3, 6); and e) infusion of epinephrine elicits the same pattern of immune responses as that seen during mental stress (8–10). Finally, results of one recent study suggest that the increase in peripheral NK cell numbers typically observed under acute stress may be inhibited by oral administration of the β-adrenoceptor antagonist, propranolol (11). Unfortunately, the latter investigation did not report the CD4:CD8 cell ratio, which is ordinarily reduced in such studies, nor did the investigation demonstrate a stress-induced suppression of mitogen-stimulated T cell proliferation against which to evaluate effects of adrenergic-blockade. In this report, we further investigate the potential sympathoadrenal mediation of stress-evoked alterations in circulating lymphocyte populations, T lymphocyte mitogenesis, and NK cell

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Received for publication April 11, 1994; revision received October 18, 1994.

0033-3174/95/5704-0366$03 00/0

cytotoxicity by the intravenous administration of the combined α- and β-adrenoceptor antagonist, labetalol.

METHODS

Subjects

Subjects were 52 healthy male volunteers (aged 18–30 years), recruited from university advertisements. All subjects were of normal weight, were nonsmokers, and reported taking no medications and consuming fewer than 10 alcoholic beverages per week. In a 2 × 2 factorial design, subjects were randomly assigned to either a "stress" or "no stress" condition, and, within each of these conditions, were administered either labetalol or saline (placebo). All subjects rested for 30 minutes before: a) a 15-minute period subsuming the infusion procedure and postinfusion baseline measurements; and b) an 18-minute task period. In vitro measurements of cellular immune function were obtained at the end of each rest and task period (i.e., three time points) as were subjects' responses to the Profile of Mood States (POMS) questionnaire. Heart rate (HR) and blood pressure (BP) were also assessed at the pre-experimental and postinfusion baseline periods and during subjects' task performance. Identical measurements were obtained among unstressed controls, although these subjects were not exposed to the experimental stressor. All subjects gave informed consent to participate in this investigation, which was approved by the Biomedical IRB of the University of Pittsburgh.

Procedures

Subjects abstained from food, caffeine, and exercise for 12 hours before participation. On arrival at the laboratory, subjects assumed a semi-recumbent position, and an intravenous catheter was inserted into the antecubital fossa of the subject's nondominant arm for the collection of blood samples and the infusion of labetalol or saline. An opaque curtain, drawn across the nondominant arm, prevented the subject from viewing these procedures. After catheter insertion, an occluding cuff was placed on the subject's dominant arm and connected to a vital signs monitor (Critikon Dinamap 8100) for automated measurement of HR (in beats per minute (bpm)) and systolic and diastolic blood pressure (SBP, DBP in mm Hg). Subjects then rested for 30 minutes, during the last 10 minutes of which HR and BP (five readings) were recorded. At minute 28, 10 ml of blood was drawn for the determination of immune parameters.

Subjects were then instructed to rest for an additional 15 minutes. At this point, each subject received, intravenously, either 0.75 mg/kg labetalol or 12 cc of saline. Labetalol was administered over two 2-minute intervals, beginning at the onset and at the fifth minute of the period. Heart rate and blood pressure were recorded during the last 4 minutes, and a second 10-ml blood sample was collected at the end to establish postinfusion baselines.

After baseline, unstressed controls were instructed to continue to rest quietly for the remainder of the study, while the stress group performed an 18-minute task consisting of: a) a modified Stroop color-word interference test (8 minutes) (3); b) mental arithmetic (5 minutes of consecutive 1 to 3 digit addition/subtraction problems); and c) simulated public speaking (5 minutes). The latter task consisted of 2 minutes of preparation for a speech in defense of a hypothetical shoplifting charge, followed by 3 minutes of videotaped speech delivery (12). Heart rate and blood pressure were again measured at 2-minute intervals throughout. An additional blood sample (10 ml) for the determination of immune indices was taken immediately after the task period from both stressed subjects and unstressed controls.

Subjective Stress Measures

A modified version of the POMS (13) was used to assess subjective responses after the pre-experimental, postinfusion baseline, and task periods. For each item, subjects were asked to indicate how they felt, using a 5-point intensity scale ranging from 0 = "not at all" to 4 = "extremely." The modified POMS consists of 25 mood adjectives, and responses yielded subscale scores along seven dimensions: fatigue, anger, anxiety, depression, vigor, well being, and calm. Internal consistencies among subscales have been found to be high (Chronbach's αs = .836 to .939).

Immune Measures

Both functional and enumerative assays were performed for immune assessment. Immune assays included lymphocyte proliferative responses to phytohemagglutinin (PHA) and concanavalin A (Con A), natural killer cell cytotoxicity, and numbers of circulating lymphocyte populations.

Mitogen stimulation. A whole blood assay was conducted to establish dose response curves for PHA and Con A at final concentrations of 2.5, 5.0, and 10.0 ug/ml. Blood was diluted 1:10 with RPMI-1640 tissue culture medium, supplemented with 10 nM of HEPES, 2 mM of glutamine, and 50 ug of gentamicin per ml. One hundred microliters of diluted whole blood was added to a 96-well, flat-bottomed culture plate containing 100 ul of PHA solution prepared in RPMI in one of the four final concentrations. Background proliferation was measured by incubating cells in RPMI only. Each assay was performed in quadruplicate. Plates were incubated for 120 hours at 37°C in air and 5% CO_2. Eighteen hours before the end of incubation, the wells were pulsed with 1 uCi of tritiated thymidine and were harvested for counting. Response was defined as the difference in counts per minute between stimulated and unstimulated samples, determined separately for each concentration. Peak mitogenic responses were found at 5 ug/ml and 10 ug/ml for PHA and Con A, respectively. Analyses here were based on these optimal concentrations, because analyses including either a single, optimal concentration of mitogen or several mitogen concentrations (as in a repeated-measures analysis) have been shown to yield similar results (14).

Natural killer cell activity. Natural killer cell function was assessed using an erythroleukemic cell line, K562, maintained in supplemented RPMI plus 15% fetal bovine serum in a CO_2 incubator. On the day of the assay, K562 targets were labelled with 100 uCi of sodium chromate-51 (Cr^{51}) for 1 hour. K562 cells were washed four times to remove exogenous CR51. One hundred and fifty microliters of diluted whole blood were plated in triplicate at 10.0, 5.0, 2.5, and 1.25×10^5 cells/well of a 96-well plate. The labeled targets were then diluted and plated at 1×10^4 cells/well. Effector:target ratios of 100:1, 50:1, and 25:1 were obtained. The plates were centrifuged at 400 g for 10 minutes and were incubated for 4 hours at 37° in air and 5% CO_2 before harvesting and counting. Natural killer cell cytotoxicity was expressed as cytotoxicity units (CU).

Lymphocyte subsets. Circulating populations of T lymphocyte subsets, B lymphocytes, and NK cells were assessed in whole blood using dual color fluorescence analysis with a FACScan flow

cytometer. Lymphocyte subsets were analyzed using monoclonal antibodies labeled with either fluorescein (FITC) or phycoerythrin (PE) to quantify CD3+CD4+ (T helper), CD3+CD8+ (T suppressor/cytotoxic), CD3-CD19+ (B), and CD3-CD16+CD56+ (NK) cells. Isotype controls labeled with FITC or PE were used to assess nonspecific binding. Absolute numbers of cells were calculated from the complete blood count.

Baseline Evaluation and Statistical Analyses

Baseline comparisons. Before statistical analysis, HR and BP data were reduced by calculating mean values for the pre-experimental, postinfusion baseline and task periods. Two subjects were omitted from analysis because of clotting or an elevated white blood cell (WBC) count[1], leaving a total of 25 subjects among the two stress conditions and 25 controls.[2]

Preliminary analyses were conducted to explore potential group differences in each of the dependent measures before task onset. For this purpose, comparisons were performed on postinfusion baselines because these values reflected any baseline adjustments incurred by labetalol infusion and were thus indicative of subjects' physiologic and psychologic states immediately preceding task exposure. Postinfusion baseline HR, BP, and immune parameters were analyzed by 2 × 2 ($Stress_{stress,control}$ × $Drug_{saline,labetalol}$) analyses of variance (ANOVA). By comparison with the saline condition, subjects given labetalol had a lower SBP and higher NK cell cytotoxicity and CD4:CD8 cell ratio (drug main effects: $Fs(1, 46) > 6.50$, $ps < .02$). Postinfusion baselines did not differ as a function of stress, drug, or the Stress × Drug interaction for any other physiologic variable.

To determine whether the baseline differences in SBP, NK cell cytotoxicity, and the CD4:CD8 ratio were attributable to labetalol infusion, or alternatively, reflected pre-existing group differences, 2 × 2 × 2 ($Stress_{stress,control}$ × $Drug_{saline,labetalol}$ × $Period_{proinfusion\ rest,\ postinfusion\ baseline}$) repeated measures ANOVAs were conducted on these variables. These analyses showed significant Drug × Period interactions for two of the three measures: SBP and NK cell cytotoxicity ($F(1,46) = 22.47$, $p = .001$; $F(1,46) = 3.88$, $p = .05$, respectively). Pairwise comparisons by Newman-Keuls' procedure revealed that SBP declined from the pre-experimental to postinfusion measurements ($\bar{X}s = 121.7$ [SE = 1.4] vs. 115.0 [1.2] mm Hg, $p < .05$) and that NK cell cytotoxicity rose significantly over the same interval ($\bar{X}s = 58.6$ [6.6] vs. 72.5 [6.0] CU, $p < .05$) among subjects that were administered labetalol. No changes were observed among subjects assigned to the saline condition. Finally, analysis of the CD4:CD8 cell ratio showed only a significant Drug main effect ($F(1,45) = 8.55$, $p < .006$), reflecting a higher CD4:CD8 ratio at baseline in the labetolol condition (2.0 [SE=.14]) than among subjects administered saline (1.6 [SE=.08]).

Affect (POMS) scales at the postinfusion baseline were markedly skewed; hence, potential baseline differences between the two stress and drug conditions were independently tested using the Mann-Whitney U procedure. Results showed no differences in baseline affect between subjects assigned to the two stress and drug conditions, nor did inspection of median values for each cell suggest any interactions of stress and drug condition on baseline affect.

Analyses of Stress- and Drug-related Changes

Quantification of task responses. Because labetalol administration was shown to alter some resting cardiovascular and immune parameters, residualized task values resulting from the regression of task measurements onto corresponding postinfusion baselines were computed to derive a covariance (i.e., baseline) adjusted task score for each cardiovascular and immunologic variable. Base line affect measures failed to conform to normal distributions and were therefore not amenable to residual analysis. Because affect measures were unaffected by labetalol administration, however, arithmetic change scores, reflecting postinfusion baseline-to-task changes, were computed for each POMS subscale.

Statistical analyses. To test the effects of stress and drug exposure on each of the dependent variables, two types of statistical analyses were performed: those for which a priori hypotheses were tested and those which were exploratory. In the first category were the analysis of HR and all measures of immune response. It was predicted that adrenoceptor blockade would attenuate both HR and immune reactions to mental stress and therefore that task values would be altered by stress only in the saline-stress condition. Because analysis of variance does not provide optimal power to detect monotone interactions (i.e., where one cell differs from the remaining three), a preplanned two-contrast procedure was employed here, as recommended by Bobko (16). *Contrast 1* (a planned comparison one-way analysis of variance) tested for the equality of the mean residualized scores of the three groups that were predicted not to differ from one another: the labetalol-stress, labetalol-control, and saline-control groups. *Contrast 2* (a planned comparison *t* test) tested for potential differences between the mean task value of the saline-stress group and a mean score derived from collapsing across the other three conditions. Our hypotheses were supported when: a) no reliable differences were obtained between the three conditions compared in Contrast 1 and b) a significant difference exists between these three groups and the saline-stress condition (Contrast 2). In instances where Contrast 1 did yield a significant effect, a 2 × 2 ($Stress_{stress,control}$ × $Drug_{labetalol,saline}$) ANOVA was conducted to further clarify potential differences among the four group means. Pairwise comparisons among means were performed using the Newman-Keuls' procedure.

In analyses of affect (i.e., POMS scores), for which no specific hypothesis had been declared, 2 × 2 (Stress × Drug) ANOVAs were used to determine the effects attributable to stressor and drug. The same analyses were also conducted on BP measurements, due to a lack of substantial evidence that adrenoceptor antagonists attenuate BP responses to acute mental stress (17). For all analyses, α level for two-tailed = .05.

RESULTS

Heart Rate and Blood Pressure

To establish the efficacy of sympathetic blockade during the task period, we first evaluated subjects' HR responses to the experimental stressor. Mean

[1] The WBC for this subject was 12.6×10^3/ml; at the University of Pittsburgh Medical Center laboratory, normal range for adult males is 4.5 to 11.0×10^3 WBC/ml.

[2] For one additional subject (saline-control), numbers of lymphocyte subpopulations are missing because of technical difficulties with the flow cytometer.

residualized scores for HR for the four groups are shown in Table 1. The Contrast 1 analysis showed that task HRs differed significantly among the three groups subject to comparison ($F(2,34) = 9.32$, $p < .001$), with the labetalol-stress group exhibiting a higher task HR response than either of the two control conditions ($ts = 2.42, 4.76$, $ps < .03$). Consequently, the 2 × 2 analysis of variance was conducted, resulting in a significant Stress × Drug interaction, ($F(1,46) = 5.57$, $p < .02$). Pairwise comparisons showed that baseline-adjusted HRs were significantly higher during the task among saline-stressed subjects than in the labetalol-stress and no-stress groups (i.e., as predicted, labetalol attenuated the HR response to stress), $ps < .05$.

In contrast to HR, stressed subjects, regardless of drug condition, showed significant and comparable elevations in blood pressure, as reflected by main effects for Group in the ANOVAs for both SBP and DBP ($Fs(1, 46) = 75.86$ and $= 69.09$, $ps = .0001$) (Table 1).

Affect

With respect to self-reported affect, analyses of variance revealed significant main effects of Stress on baseline-to-task changes in Anxiety ($\bar{X}\Delta = 1.32$ (Stress) vs. −0.3 (Control), Anger (0.41 vs. 0.04), Vigor (1.45 vs. −0.01), Depression (0.23 vs. 0.00), Fatigue (−1.05 vs. −0.01), and Calm (−1.64 vs. −0.08); for all scales: $Fs(1, 46) > 4.00$, $ps < .05$. There was no similar main effect of Stress for reported well being, nor did any affect measure reveal a significant main effect of Drug or Stress × Drug interaction.

Immune Measures

The variables of greatest interest in this study were the assessments of circulating lymphocyte numbers and function. For all immunologic measures, comparisons in Contrast 1 were nonsignificant: $F(2,33) = 1.44$; $F(2,33) = 1.16$; $F(2,33) = .49$; $F(2,33) = 2.0$; $F(2,33) = .03$; $F(2,33) = .07$, $F(2,34) = .05$; $F(2,34) = 1.49$; and $F(2,34) = 2.80$ for numbers of NK, CD3, CD4, CD8, CD19, and CD4:CD8 lymphocytes, PHA and Con A mitogenesis, and NK cell cytotoxicity, respectively. Subsequent Contrast 2 analyses for both the CD4:CD8 cell ratio and NK cell number indicated that the saline-stress condition differed significantly from the remaining three groups (for CD4:CD8, $t = 2.07$, $p = .05$; for NK cells, $t = -6.49$,

TABLE 1. Mean Heart Rate, Blood Pressure, Lymphocyte Subsets and Proliferative Responses to PHA and Con A by Experimental Condition, Adjusted for Postinfusion Baseline[a]

	Experimental Condition			
	Saline/Stress	Labetalol/Stress	Saline/Control	Labetalol/Control
Cardiovascular measures				
Heart rate (bpm)	74.35	64.16	59.81	57.52
	(2.65)	(1.22)	(1.33)	(0.74)
Systolic BP (mm Hg)	132.52	131.12	120.07	116.29
	(2.09)	(1.56)	(1.31)	(1.06)
Diastolic BP (mm Hg)	74.36	74.61	64.51	62.67
	(1.56)	(1.70)	(1.04)	(.72)
Immunologic measures				
PHA (5 ug/ml)(cpm × 10^3)	904.14	1129.34	1142.11	1166.89
	(40.90)	(124.33)	(76.15)	(43.57)
Con A (10ug/ml)(cpm × 10^3)	479.30	569.58	558.03	630.96
	(25.69)	(40.90)	(25.77)	(29.93)
NK cell cytotoxicity (CU)	91.74	76.51	66.94	61.52
	(7.55)	(4.36)	(3.83)	(5.20)
NK cells (cell/mm^3)	464.39	279.26	249.24	237.06
	(44.72)	(21.26)	(22.02)	(11.43)
CD4:CD8 cells	1.63	1.77	1.81	1.80
	(.07)	(.04)	(.10)	(.08)
CD8 cells	451.84	426.47	364.45	417.51
	(34.42)	(25.46)	(26.18)	(18.14)
CD4 cells	604.18	661.55	620.56	663.30
	(29.44)	(36.68)	(42.56)	(22.58)
CD3 cells	1096.54	1094.54	988.19	1088.45
	(76.03)	(62.86)	(53.59)	(45.24)
CD19 cells	245.33	266.09	261.27	265.20
	(8.86)	(20.51)	(9.40)	(10.69)

[a] *SE of the means are in parentheses.*

$p < .001$). As indicated in Table 1, the saline-stress group exhibited an appreciably lower CD4:CD8 cell ratio under stress than did labetalol-stress and control subjects. NK cell numbers were *higher* in the saline-stress condition, and indeed, exceeded those of stressed subjects administered labetalol by 66 percent. Contrast 2 comparisons for the remaining cell populations (i.e., CD3, CD4, CD8, and CD19 lymphocytes) were not significant (ts = −.57, 1.193, −1.612, 1.266, respectively, all not significant).

Analyses for NK cell cytotoxicity and proliferative responses to PHA and Con A also revealed significant differences between the saline-stress condition and all other groups (Contrast 2: NK cell cytotoxicity: t = −3.72; PHA: t = 2.78; Con A: t = 3.03, *ps* < .01) (Table 1). As expected, T cell proliferation in response to PHA and Con A was significantly lower under stress in the saline-stress condition that among the three other subject groups. As with the number of NK cells, subjects in the saline-stress condition also showed *higher* NK cell cytotoxicity, relative to the other groups. To assess NK cytotoxicity independent of the concomitant rise in peripheral NK cells, contrast analyses were repeated, with NK cytotoxicity adjusted for both postinfusion baseline and (residualized) task scores for NK cell number. These analyses revealed no differences in NK cell cytotoxicity among any of the subject groups, after controlling for numbers of NK cells (contrast 1: $F(2,33) = 1.853$; contrast 2: t =−.207, all not significant).

DISCUSSION

The purpose of this investigation was to determine whether sympathoadrenal activation influences the cellular immune alterations most typically observed under acute mental stress. Consistent with previous research, circulating NK lymphocytes were increased in number and both the CD4:CD8 cell ratio and the mitogenic responses to PHA and Con A were diminished after mental stress among autonomically intact (i.e., saline-stressed) subjects, compared to individuals in the labetalol-stress and nonstressed conditions. Moreover, mean values in the latter three groups did not differ significantly. Thus, these findings: a) demonstrate that alterations in lymphocyte mitogenesis and in the CD4:CD8 cell ratio seen in human subjects during mental stress are dependent on concomitant sympathetic activation; and b) support an earlier report that stress-induced changes in NK cell numbers may be blocked by adrenergic inhibition (11). Stressed subjects administered saline also showed greater NK cell cytotoxicity after the task. However, these results were not significant after adjustment for the concomitant rise in NK cell numbers, indicating that the enhanced cytotoxicity seen during mental stress was secondary to the expanded NK cell population (11).

The stressor in this experiment evoked increases in negative affect and task engagement, as well as decreases in reported calm and fatigue. Previously it has been reported that β-blockers may reduce anxiety during mental stress (17), suggesting the possibility that diminished negative affect under adrenergic blockade might account for the attenuated immunologic reactions to stress seen here. However, our findings are not consistent with this hypothesis because subjective reactions to the task were comparable in the two stressed groups, irrespective of drug administration.

Although our results demonstrate the sympathetic modulation of immune reactions to mental stress, they do not identify the more specific mechanism(s) underlying this association. Lymphocytes have adrenergic receptors and reside in close proximity to sympathetic nerve endings in lymphatic tissue. Thus, one mechanism is likely to involve direct interactions between the catecholamines and lymphocytes. For example, blood-borne lymphocytes enter some lymphoid organs by first attaching, via adhesion molecules, to specialized endothelial cells lining the postcapillary venules of lymphatic tissue. Catecholamines may alter the expression of surface adhesion molecules on lymphocytes and the endothelium and thereby inhibit migration of peripheral lymphocytes into lymphoid organs (18). Consistent with this hypothesis, recent studies indicate that catecholamines prevent the adherence of human NK lymphocytes to endothelial tissue in vitro (19). Another potential mechanism relates to the extrusion of stored lymphocytes from spleen to periphery by contraction of smooth muscle surrounding the spleen. Indeed, it has been reported that, in rabbits, infusion of epinephrine causes splenic contraction and the release of lymphocytes from both the spleen and bone marrow to the peripheral blood, heart, lungs, and liver (20). To the extent that lymphocyte population responses to stress were effectively blocked by labetalol in the absence of any reduction in blood pressure reactivity, the current findings suggest that immune responses to acute stress are not mediated by hemodynamic factors.

In humans, changes in circulating populations of lymphocytes during mental stress reflect alterations in migration between the peripheral blood and lym-

phoid organs, as opposed to the de novo generation or destruction of such cells (21). It is not yet clear why migratory changes, induced by sympathetic activation, typically involve some lymphocyte populations and not others (e.g., B cells). Recent evidence indicates that lymphocytes differ in both β-receptor density and the generation of cyclic adenosine monophosphate (cAMP) after adrenergic stimulation. It has been reported, for instance, that CD8 and NK lymphocytes have a moderately high β-receptor density and cAMP production, whereas CD19 lymphocytes have a high β-receptor density but show a comparatively weaker generation of cAMP (22). In addition, lymphocyte populations reside in distinct locations of the lymphoid organs, with some subtypes (e.g., the T cells) more proximal to both the vasculature and sympathetic innervation than others (e.g., the B cells) (7). In part, then, T cells may be more vulnerable to adrenergic influences than B lymphocytes by virtue of their location within lymphatic tissue. Finally the activation state of B cells may be an important factor, because activated B lymphocytes have been shown more responsive to β-adrenergic stimulation than inactivated cells in vitro (23).

The adrenergic mechanism(s) mitigating proliferative responses during stress are also unclear, but may involve the regulation of particular receptors and cytokines necessary for mitogenesis. For example, T cell proliferation requires the expression of surface interleukin-2 (IL-2) receptors on activated lymphocytes and the release of IL-2 by CD4 lymphocytes. Of interest, it has been shown that examination stress reduces the expression of IL-2 receptors on lymphocytes (24–25) and that catecholamines, in vitro, suppress IL-2 production (26), the expression of IL-2 receptors (26), and IL-2-stimulated lymphocyte proliferation (27).

In conclusion, we have reported experimental evidence indicating the sympathoadrenal modulation of select immune responses to acute mental stress. Further research is needed to determine the specific mechanism(s) underlying these associations, as well as to assess the impact of sympathetic activation on protracted changes in immune function resulting from exposure to more *chronic* forms of psychological stress (28).

This research was supported, in part, by Grant IRG-58–31 from the American Cancer Society and by NIH Grant HL 40962 (SBM).

Special thanks to T. Fazzari, J. Fulton, C. Martin, and K. Weber for their technical assistance.

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