Effects of β-Adrenergic Blockade on Immunologic and Cardiovascular Changes Induced by Mental Stress

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Background  Acute mental stress evokes responses in the cardiovascular and the immune systems. In particular, the subset of natural killer (NK) cells is found to be responsive to mental stress. The role of β-adrenergic mechanisms in these processes is the subject of this investigation.

Methods and Results  Healthy male volunteers (n=31) were subjected to two consecutive mental tasks. Subjects were randomly assigned to a β-blocker (propranolol 40 mg) or a placebo group. The capsules were ingested 1 hour before the tasks. The tasks evoked sympathetic responses, as indicated by an increase in heart rate and a decrease in the pre-ejection period. These effects were abolished under β-blockade, indicating that effective β-blockade was achieved. In the immune system, significant increases were found for the number of NK cells and NK cell activity in the placebo group; these increases were absent in the propranolol group. In addition, an increase in all lymphocyte subsets was observed in subjects who had ingested propranolol. This increase, however, was also observed in subjects who had received propranolol but had not performed the tasks, indicating that these non-subset-specific increases in lymphocytes were a side effect of the β-blocker.

Conclusions  Mental stress induces activation of the sympathetic nervous system, with concomitant increases in the number of NK cells in the circulation. These changes were inhibited by propranolol, indicating that stress-induced increases in the number and activity of NK cells in the circulation are controlled by a β-adrenergic mechanism. (Circulation. 1994;89:762-769.)

Key Words  • lymphocytes  • cells

Many studies have shown that acute mental stress is accompanied by rapid and transient increases in cardiovascular variables like blood pressure and heart rate.1-7 These heart rate responses can be inhibited by prior administration of β-antagonists, indicating that mental stressors activate the β-adrenergic system.2-4 It has repeatedly been shown in other studies that acute mental stress also affects parameters of the immune system,6-12 parallel to the effects on the cardiovascular system. As a result, the number and activity of natural killer (NK) cells in peripheral blood increases significantly. NK cells play a prominent role in combating viral infections and are important in the first line of defense.13,14 The increase in NK cell numbers in the circulation is transient,15,16 similar to the changes in cardiovascular variables.

To date, it is unknown whether the effects of acute mental stress on the immune system are also related to β-adrenergic mechanisms. A direct relation between β-adrenergic stimulation and the increase in the number of NK cells has been inferred from studies in which β-agonists were infused.16-19 In addition, it was shown earlier that physical exercise, which leads to increased catecholamine levels, also affects immune parameters (see McCarthy and Dale20 for a review). It should be noted, however, that physical exercise not only influences the number of NK cells but also causes a strong increase in the number of T and B lymphocytes.21 These transient changes in immune variables could be inhibited, at least partially, by prior administration of β-antagonists.21,22 A direct comparison with the effects of mental stress is difficult, since physical exercise results not only in an increase in the concentration of catecholamines but also in changes of the levels of many other hormones.23,24

In the present placebo-controlled, double-blind study using the nonselective β-antagonist propranolol, we investigated whether β-adrenergic mechanisms mediate the immunologic responses to acute mental stress. We examined several aspects of the immune system (ie, lymphocyte subset distribution and functional parameters of cellular immunity). Cardiovascular variables were monitored to check whether the responses to the tasks were mainly sympathetic in nature and to examine the effectiveness of the β-blockade.

Methods

Subjects

All subjects participating in the experiments were nonsmoking, healthy males, ranging in age from 18 to 32 years (mean, 23.4 years). Participants were subjected to a general medical and cardiologic examination to ensure that they were free of any current or chronic serious ailments. Standard procedures were followed at the time of invitation: subjects were instructed to have a light breakfast, to refrain from coffee, and not to eat for 2 hours before the session. They were also
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requested not to drink alcoholic beverages nor to engage in extreme physical activity the day before the experiment. Before participating in the study, subjects completed a short questionnaire on biological data and signed a consent form. The protocol was approved by the Free University of Amsterdam Ethical Committee for investigations involving human subjects.

Experimental Protocol

Subjects were seated in a reclining chair in a dimly lit and sound-shielded room. They faced a video monitor that was placed 3 m in front of them and used a panel with four buttons to respond to the tasks presented. Electrodes for measuring the ECG and the impedance cardiogram (ICG) were attached to the subject, and a blood pressure cuff was wrapped around the nondominant upper arm. An indwelling catheter was inserted for blood sampling. After a 30-minute rest period, the first blood sample was taken (t=0). Then the subjects received propranolol tablets randomized with placebo capsules containing lactose. Both the experimenter and the subjects were unaware of the content of the capsules. For the next 60 minutes, subjects were allowed to relax and read popular magazines. This period ended with the first blood sample was taken (t=0). Then the subjects received a small plastic container labeled “propranolol 40 mg” and were asked to ingest the capsule. Propranolol tablets were placed behind cervical vertebra C4 and behind thorax vertebra T9. The basal thorax impedance (Zb) was continuously displayed and recorded by the experimenter every 2 minutes. The first derivative of the impedance signal, dZ/dt, was recorded with a time constant of 5 seconds and a high-frequency cutoff of 75 Hz. Signals were displayed on a Beckman Dynograph (R611) and digitized at 250 samples per second via a 12-bit analog-to-digital converter. Mean arterial pressure (MAP) and systolic (SBP) and diastolic (DBP) blood pressures were measured with a Dinamap vital signs monitor (Critikon model 845 XT).

Signal Processing

Heart rate was computed as the inverse of the period between successive R waves and expressed as beats per minute. ECG and ICG complexes of each 1-minute period were ensemble averaged in reference to the ECG R wave. The averaged complexes were used to compute the precession period (PEP), left ventricular ejection time (LVET), and the maximal rate of change of impedance (dZ/dtmax). PEP was defined as the time in milliseconds between Q-wave onset in the ECG and the B point in the dZ/dt signal. PEP is an index of cardiac contractility, and changes in PEP during stress are considered to reflect predominantly β-adrenergic effects on the heart.4 LVET was defined as the time between the B and the X points in the dZ/dt signal. dZ/dtmax was scored as the difference between the maximal amplitude of dZ/dt and the amplitude of the signal at the B point. dZ/dtmax and the LVET were used to calculate stroke volume (SV) using the formula proposed by Kubicek et al.20: SV = p × (Ls/Zb) × dZ/dtmax/LVET, in which p is resistivity of the blood at 100 kHz (set to a constant value of 135 Ω cm−1). Ls is the shortest distance between the measuring electrodes, and Zb is the basic thorax impedance. Cardiac output (CO) was computed by multiplying heart rate and SV. Total peripheral resistance was estimated with the formula TPR = (MAP/CO) × 80 (in dyne-seconds/cm5).

Immunologic Variables

Hematocrit and blood cell count of all samples were determined in whole blood using an automated closed-tube sampler (Technicon H-1 system). Lymphocyte subset analysis was performed by incubating 100 μL of whole heparinized blood with one of the following combinations of monoclonal antibodies (Becton-Dickinson, Mountain View, Calif): CD4/CD8, CD3/HLA-DR, and CD56. Next, red blood cells were lysed (lysing solution, Becton-Dickinson) and washed twice with phosphate-buffered saline containing 0.5% bovine serum albumin and 0.1% sodium azide, after which they were analyzed with a flow cytometer (FACScan, Becton-Dickinson).

Natural killer cell activity (NKCA) was determined in heparinized whole blood, with some modifications to the original protocols.27,28 K562 was used as the target cell line: cells were labeled with 51CrNa2CrO4 (3.7 MBq; Amersham, UK) for 1 hour at 37°C, 5% CO2. After labeling, cells were washed twice, counted, and resuspended in RPMI-1640 (Gibco, UK) supplemented with penicillin (100 IU/mL), streptomycin (100 μg/mL), L-glutamine (2 mmol/L), and β-mercaptoethanol, hereafter referred to as “medium.” Undiluted whole blood (100 μL) and three serial 1:1 dilutions in medium were dispensed into wells of a 96-well round-bottom tissue culture plate. A fixed number of labeled K562 cells were added to each well (100 μL; 6250 K562 cells per well). The results reported here are from undiluted whole blood; similar results were obtained with the lower dilutions or when more K562 cells were used (12 500 cells per well; unpublished observations). Plates were centrifuged for 5 minutes (100g) and incubated at 37°C, 5% CO2. After 4 hours, plates were centrifuged again (5 minutes, 100g), and supernates (100 μL) of triplicate samples were counted in a gamma counter for 1

Cardiovascular Measurements

Signal Recording

ECG Ag/AgCl electrodes were placed on the sternum, the lateral margin of the chest, and in the right lower quadrant. The ICG was recorded with a Nihon Kohden impedance cardiograph using four Ag/AgCl spot electrodes.25 The current electrodes were placed behind cervical vertebra C4 and behind thorax vertebra T9. The measuring electrodes were placed 4 cm above the clavicle on the front of the neck and over the sternum at the fourth rib. The basal thorax impedance (Zb) was continuously displayed and recorded by the experimenter every 2 minutes. The first derivative of the impedance signal, dZ/dt, was recorded with a time constant of 5 seconds and a high-frequency cutoff of 75 Hz. Signals were displayed on a Beckman Dynograph (R611) and digitized at 250 samples per second via a 12-bit analog-to-digital converter. Mean arterial pressure (MAP) and systolic (SBP) and diastolic (DBP) blood pressures were measured with a Dinamap vital signs monitor (Critikon model 845 XT).
minute. Maximum $^{3}$Cr release and spontaneous release were determined in wells containing 1% Triton-X or medium, respectively. Specific $^{3}$Cr release was calculated as follows: % release = $[(ER-\{V_{t}-(V_{s} \times H)\}/V_{s}) \times SR] \times (TR-TR) \times 100$, where ER = mean cpm experimental release, SR = mean cpm spontaneous release, TR = total release, V$_{t}$ = total volume in well, V$_{s}$ = volume of blood in well, and H = hematocrit.

Proliferative responses of peripheral blood mononuclear cells were tested according to the method described by Bloemen et al.$^{29}$ Heparinized blood was diluted 10 times with medium, and 150 μL of the diluted blood was incubated with phytohemagglutinin (PHA, 50 μL; Wellcome Diagnostics, UK) in three concentrations (final concentrations, 10, 20, and 40 μg/mL). Proliferative responses were determined after 3 days of culture (37°C, 5% CO$_{2}$) by measuring incorporation of $[^{3}$H$]$/thymidine added 16 to 18 hours before the harvest of the culture. All cultures were performed in triplicate.

**Statistical Analyses**

Differences in responses between groups (placebo or propranolol) during the experimental period were tested as interactions of group by time, with ANOVA for repeated measures. Three time points were included in these analyses: for immunologic variables, these were pretask (t=60), immediately after the tasks (t=90), and at the end of the session (t=135); for cardiovascular variables, the second time point represents the mean response, averaged over the two tasks. Averaged tests of significance were used, with Greenhouse-Geisser correction of degrees of freedom. Post hoc analyses (Student’s t test) were performed when the groups differed significantly in their response (ie, when a significant group × time interaction was found) to see which point(s) explained the group differences. The first time point (t=0, before ingestion of the capsule) was used to check for preexisting differences between the placebo and the propranolol group (Student’s t test).

**Results**

**Levels Before the Tasks**

First, we examined preexisting differences between the placebo and the propranolol group. The groups did not differ in biobehavioral characteristics (ie, normal physical activities and average alcohol and coffee intake). At the time of ingestion of the capsule (t=0), no statistically significant differences were found with regard to the immunologic variables nor for any of the cardiovascular variables with the exception of PEP, which was significantly longer in the propranolol group ($t$[28]$=-4.4, P<.01$; Fig 1). One hour after ingestion of the capsule (t=60), no group differences had yet occurred, except again for the difference in PEP, which was still longer in the propranolol group ($t$[28]$=-3.3, P<.01$; Fig 1). In the period between ingestion of the capsule (t=0) and just before the tasks (t=60), SBP, NKCA, and the number of CD56+ cells significantly decreased, whereas PEP increased, but this occurred to a similar extent in both groups (see Figs 1 and 2). The changes in these variables can be seen as an indication that the subjects relaxed during this period.

**Effects of Mental Stress**

**Cardiovascular Measurements**

Amplitude and patterning of the cardiovascular responses were similar for both mental tasks in both groups (Fig 1). Therefore, the mean response, averaged
over the two tasks, was used in the statistical analyses. The heart rate response was significantly smaller in the propranolol group (group \times time: F(2,56)=13.2, P<.001; Fig 1). Post hoc analyses showed that the groups differed significantly during the tasks (t[28]=3.2, P<.01) and at the end of the session (t[28]=2.9, P<.01). Heart rate increased in the placebo group, whereas no change in heart rate was observed in the propranolol group. Directly after the stressors (t=95) and at the end of the session (t=135), heart rate was significantly lower in the propranolol group (Fig 1), obviously the effect of the \( \beta \)-blocker. PEP decreased significantly in response to the tasks in the placebo group but remained unchanged in the propranolol group (F[2,54]=9.2, P<.001; Fig 1).

For SBP and DBP, no significant group \times time effects were found, which indicated that the subjects in both groups responded with an equal increase in blood pressure (Fig 1). The means by which these blood pressure increases were accomplished, however, were completely different in the two groups. Total peripheral resistance increased by 101.5\% (compared with t=0) in the propranolol group and remained unchanged in the placebo group (F[2,48]=13.6, P<.001; data not shown). Opposite responses were seen for CO: CO increased by 26.6% in the placebo group and decreased by -29.8% in the propranolol group (F[2,54]=15.3, P<.001; data not shown). These changes resulted in similar blood pressure responses in the placebo and the propranolol groups.

**Immunologic Variables**

Significant differences in responses between the placebo and the propranolol groups were found for CD56+ cells (F[2,58]=19.4, P<.001) and NKCA (F[2,58]=13.4, P<.001; Fig 2). In the placebo group, the tasks evoked a substantial increase in the number of CD56+ cells and NKCA, followed by a return to pretask values at the end of the session. No such response was seen for subjects in the propranolol group. Post hoc analyses showed a group difference immediately after the tasks (t=90) for the number of CD56+ cells (t[29]=3.7, P<.01) and NKCA (t[29]=2.2, P<.05). When the specific activity per single NK cell was calculated, we found no changes over time. This was confirmed by ANCOVA with repeated measures, using the absolute numbers of NK cells as the covariate: after NK cell numbers were controlled for, the alterations in NKCA over time were no longer significant (data not shown).

Other significant differences in the responses between the placebo group and the propranolol group were found for all lymphocytes (F[2,58]=9.6, P<.001) and the subsets of CD8+ cells (F[2,58]=19.0, P<.001), CD3+ cells (F[2,58]=7.4, P<.01), and CD4+ cells (F[2,58]=4.7, P<.05; summarized in the Table). All these variables shared a similar pattern of change, illustrated for lymphocytes and CD8+ cells in Fig 2, that was different from the one found for CD56+ cells and NKCA. Post hoc analyses showed that, now, the group differences were caused not by the values immediately after the tasks (as found for CD56+ cells and NKCA) but rather by the recovery values at the end of the session at t=135 (all lymphocytes, t[29]=2.3, P<.05; CD3+ cells, t[29]=2.9, P<.01; CD4+ cells, t[29]=2.0, P<.05; CD8+ cells, t[29]=2.1, P<.05). This indicates that in the propranolol group, an increase is observed...
Values of Immunologic Variables of the Placebo and Propranolol Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time, min</th>
<th>Placebo (n=16)</th>
<th>Propranolol (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes x 10^6/L†</td>
<td></td>
<td>1.5±0.10</td>
<td>1.63±0.13</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>1.47±0.09</td>
<td>1.58±0.10</td>
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<tr>
<td></td>
<td>90</td>
<td>1.78±0.11</td>
<td>1.80±0.12</td>
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<td></td>
<td>135</td>
<td>1.54±0.09</td>
<td>1.86±0.10</td>
</tr>
<tr>
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<td>1.02±0.07</td>
<td>1.15±0.10</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>0.97±0.07</td>
<td>1.11±0.08</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>1.07±0.07</td>
<td>1.25±0.10</td>
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<tr>
<td></td>
<td>135</td>
<td>1.01±0.07</td>
<td>1.32±0.08</td>
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<tr>
<td>CD4+ x 10^6/L*</td>
<td></td>
<td>578±42</td>
<td>645±63</td>
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<td></td>
<td>60</td>
<td>582±47</td>
<td>667±62</td>
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<tr>
<td></td>
<td>90</td>
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<td>763±72</td>
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<tr>
<td></td>
<td>135</td>
<td>606±52</td>
<td>761±59</td>
</tr>
<tr>
<td>CD8+ x 10^6/L†</td>
<td></td>
<td>462±41</td>
<td>500±63</td>
</tr>
<tr>
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<td>472±45</td>
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<td></td>
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<tr>
<td>CD56+ x 10^6/L†</td>
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<td>135</td>
<td>208±18</td>
<td>248±27</td>
</tr>
<tr>
<td>B cells x 10^6/L‡$</td>
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<td>262±36</td>
</tr>
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<tr>
<td></td>
<td>135</td>
<td>309±26</td>
<td>299±38</td>
</tr>
</tbody>
</table>

Values are mean±SEM. The capsule was given at t=0, and the stressor was applied between t=60 and t=90.

Significant two-way interactions (group x time) for t=60, 90, and 135: *P<.05; †P<.01; ‡P<.001; §P=NS.

during the course of the experiment for all lymphocyte subsets, which becomes evident after tasks at t=90 and continues through to the end of the experiment (at t=135). A similar pattern can also be observed for CD56+ cells and NKCA in the placebo group (Fig 2), but it is less striking because of the large stress-induced increase in these variables in the placebo group. From the data in the Table, it can be inferred that the increase in the number of lymphocytes in the placebo group can be accounted for almost entirely by increases in the subset of CD56+ cells.

Proliferative responses of peripheral blood mononuclear cells to PHA were concentration dependent, with half-maximal responses to the lowest dose (10 μg/mL). These proliferative responses were not affected by propranolol treatment itself, nor did proliferation to any of the three concentrations change in response to the stressor (data not shown).

Propranolol Increases Lymphocyte Numbers in a Non–Subset-Specific Manner

To test whether the observed changes in immunologic variables in the propranolol group were due to the tasks or to a nonspecific effect of the β-blocker, we tested the effects of propranolol in an additional group of 11 subjects without mental tasks. These subjects also randomly received either a placebo (n=5) or a propranolol (n=6) capsule, and blood parameters were monitored as before. Subsequently, we tested whether the changes for the immunologic variables were different in the propranolol group of the original experiment (in the presence of mental tasks) versus the propranolol group in this control experiment (no task). ANOVAs for repeated measures using the sampling points t=60, t=90, and t=135 revealed no differences between the task and the no-task groups for any of the immune variables for the subjects who had ingested the propranolol capsule (Fig 3). In contrast, in the group of subjects who had taken the placebo capsule, the no-task group differed significantly from the task group for total lymphocytes (F[2,38]=7.7, P<.01), CD8+ cells (F[2,38]=11.9, P<.001), CD56+ cells (F[2,38]=10.1, P<.001), and NKCA (F[2,38]=11.4, P<.001). These findings are also illustrated in Fig 3, showing the changes, relative to pretask levels (t=60), at the last two sampling points. On the left side, the subjects who received placebo are shown: an apparent increase is seen in the task condition, but no changes are observed in the absence of tasks. In the subjects who had taken propranolol (shown on the right), the changes in the task and the no-task conditions are similar. These data indicate that the nonsubset-specific changes in lymphocyte numbers seen in the original experiment were caused by the β-blocker and that these changes occur independently of the tasks.

Discussion

The results in the present report show that mental stress induces changes in both cardiovascular and immunologic variables. With the exception of the blood pressure response, changes in heart rate, PEP, and immunologic variables were abolished under β-blockade. This indicates that catecholamines are involved in the rapid physiological responses that are induced by mental tasks and further suggests that the changes in the immune and cardiovascular system share the same regulatory mechanism.

In the placebo group, significant changes were found after the tasks for all cardiovascular variables: heart rate and blood pressure were markedly increased, whereas PEP was decreased. These results indicate that the stressor induces activation of the sympathetic nervous system. This has been reported before when several kinds of mental tasks were used.4,5,30 The task-induced changes of heart rate and PEP were completely inhibited by propranolol, but the blood pressure responses in this group were not different from those found in the placebo group. This is well in accordance with most other reports in the literature (reviewed by Mills and Dimsdale21) and may be related to the unopposed stimulation of α-receptors by catecholamines that are released after stress. Indeed, we found, in line with previous research,2,30 that the blood pressure response in the β-blocker group was achieved by increasing the total peripheral resistance. These data are in agreement with the theory that the autonomic nervous system is geared toward regulation of blood pressure, thereby adjusting flow and resistance.22 In conclusion, the results of the cardiovascular measurements show that the
tasks evoked a sympathetic response in the subjects and that the \( \beta \)-blockade was effective.

The circulation pattern of cells of the immune system was significantly influenced by the tasks. In line with other reports,\textsuperscript{8,10,12,15} we found that the cells that were most obviously affected had the phenotypical and functional characteristics of NK cells. The increase in NK cell numbers and NKCA was abolished by \( \beta \)-blockade, suggesting that these stress-induced changes are mediated by catecholamines. These results are congruent with studies showing the positive effect of infusion of \( \beta \)-adrenergic agonists on the numbers of NK cells in the circulation.\textsuperscript{16-18} This process is mediated by \( \beta_1 \)-adrenergic receptors rather than through \( \beta_2 \)-adrenergic receptors, since selective \( \beta_1 \)-blockade does not attenuate the exercise- or infusion-induced increase in NK cell numbers.\textsuperscript{17,21} However, the precise mechanisms underlying these increases in the numbers of NK cells or where they are recruited from are not known. The majority of NK cells reside in peripheral blood, spleen, and lung interstitium.\textsuperscript{33,34} Although the spleen is considered to be the major site for the release of lymphocytes in general (including NK cells), infusion of \( \beta \)-adrenergic agonists in splenectomized patients is still followed by an (albeit reduced) increase in the number of NK cells but not of other lymphocyte subsets.\textsuperscript{17} This indicates that NK cells can also be recruited from the other sites by \( \beta \)-adrenergic stimulation. The distribution pattern of NK cells in the body also suggests adhesive interactions with endothelial cells of the blood vessels of the venular system, in the so-called marginal zone.\textsuperscript{35} Recent experiments in vitro have shown that epinephrine specifically reduces the adhesion of NK cells to endothelium,\textsuperscript{36} thus explaining the increased number of cells in the circulation population after \( \beta \)-adrenergic activation. The release of epinephrine in acute stressful situations may be an important mechanism to rapidly recruit large numbers of immunocompetent cells from their storage sites.

Proliferative responses to PHA did not change in response to the stressor, in line with other reports.\textsuperscript{7,12} Infusion of high doses of \( \beta \)-adrenergic agonists, however, does reduce mitogen-induced proliferation.\textsuperscript{17,37} This suggests that relatively strong \( \beta \)-adrenergic stimulation is required to alter proliferative responses and that these responses are not achieved by mental stress. Even though an increase was seen in the numbers of lymphocytes after propranolol, proliferative responses did not rise significantly. This probably is because of the relatively small variation in lymphocyte numbers and the limited magnitude of change. This confirms the report by Bloemena et al.,\textsuperscript{29} who, in a large sample of subjects (\( n=700 \)), also did not find a correlation between lymphocyte numbers and proliferative responses in whole blood cultures.

It is tempting to compare the results obtained in studies using acute mental stress with those using physical exercise. Both paradigms result in activation of the sympathetic nervous system, characterized by an increase in catecholamine concentration, heart rate, and blood pressure, and lead to an increase in the number and activity of NK cells. One of the obvious differences between the two paradigms is the physical component, which is absent in mental stress. As a consequence, different and/or additional mechanisms may be activated in each situation. Physical exercise, for example, is associated mainly with the release of nor-epinephrine, whereas emotional stress leads primarily to an increase in epinephrine concentration.\textsuperscript{37,38}
over, β-adrenergic blockade only partially diminishes the tachycardia in response to exercise, whereas the tachycardia in response to mental stress is entirely abolished by β-blockade. Finally, the increase in NK cells and NKCA can only be partially inhibited by propranolol in an exercise paradigm, whereas the results of the present study show that these responses to mental stress can be entirely inhibited by propranolol. Taken together, this suggests that the physiological changes that follow mental tasks are mediated primarily by β-adrenergic mechanisms, whereas additional mechanisms play a role in the changes induced by physical exercise.

In addition to the attenuation of heart rate, PEP, and NK cell responses by propranolol, we report that administration of propranolol alone affects lymphocyte circulation, i.e., causes a non-subset-specific increase in circulating lymphocyte numbers. These increases were found to be not related to the tasks, since the pattern of change observed in the no-task group was similar to that seen in the task group. Growing evidence suggests that the sympathetic nervous system participates in control over the immune system. Therefore, it is conceivable that interference with this control by β-blockade will also influence immune parameters. Moreover, it is known that a wide range of hormones and neuroptides influence lymphocyte circulation (reviewed by Ottaway and Husband). Since propranolol will interfere with β-adrenergic regulation of lymphocyte circulation, it seems likely that, as a consequence, the effects of the other hormonal factors on lymphocyte circulation become relatively more important. There are only a few other reports dealing with the immediate effects of propranolol on the immune system: 1 week of propranolol treatment increases the number of circulating lymphocytes as well as functional immunologic parameters. What the significance of these changes is with respect to health is not clear.

In conclusion, the results of the present study show that catecholamines are important mediators of cardiovascular and immunologic responses to mental stress. The release of catecholamines in stressful situations serves to activate systems that are necessary for the defense of an organism (Cannon’s fight-or-flight concept). Under these circumstances, the regulation of optimal blood flow to the various organs is essential, which is achieved by regulating blood pressure. Detachment of immunocompetent cells (i.e., NK cells) from storage sites may be an important step in the first phase of immunologic defense. In this respect, it is interesting to notice that blockade of β-adrenergic receptors does not impede the blood pressure response to stress but does prevent the recruitment of NK cells. Therefore, it can be speculated that β-blockade interferes with the very first phase of immunologic defense in acute stress situations.

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