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β_2-Adrenergic Receptor Density and Cardiovascular Response to Mental Stress

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MARSLAND, A. L., S. B. MANUCK, P. WOOD, B.S. RABIN, M.F. MULDOON AND S. COHEN. *β_2-Adrenergic receptor density and cardiovascular response to mental stress.* PHYSIOL BEHAV **57**(6) 1163–1167, 1995.—In this study we evaluated effects of an acute experimental stressor on β_2-adrenoceptor density and examined the relationships of baseline receptor density to cardiovascular reactions induced by stress. In addition, we investigated whether any observed alterations in receptor density were associated with concomitant redistribution of circulating lymphocyte populations. Receptor density and lymphocyte subsets were determined before and immediately following performance of a frustrating laboratory task in 22 male volunteers. Blood pressure, heart rate (HR), and plasma catecholamine concentrations were also assessed at baseline and during task performance. Parallel measurements were obtained among 11 unstressed control subjects. Receptor density increased significantly between baseline and posttask measurements, but equally so in experimental and control subjects. Numbers of T suppressor/cytotoxic and natural killer cells increased selectively among subjects assigned to the experimental (stress) condition. However, there was no association between lymphocyte subset distribution and receptor density. Interindividual variability in pretask receptor density correlated significantly with heart rate and systolic blood pressure (SBP) reactivity during the initial 3 min of mental stress, but not over the entire task period. In addition, baseline receptor density correlated with SBP (but not HR) reactivity after covariance adjustment for the concomitant change in plasma catecholamine concentrations.

Experimental stress β_2-Adrenoceptor density Cardiovascular reactivity Heart rate Blood pressure Plasma catecholamine concentration

INTRODUCTION

THERE is evidence that β_2-adrenoceptor function both predicts cardiac responsivity to acute psychological stress and is itself altered following subjects' exposure to stress. For example, interindividual variability of adrenoceptor density (as measured on lymphocytes) and sensitivity (as inferred by response to infusion of agonist) has been found to covary with individual differences in behaviorally evoked heart rate (HR) and systolic blood pressure (SBP) reactivity (3,15,17). Additionally, it has been reported that receptor density increases acutely with exposure to both mental stress and infusion of sympathetic agonists (7,8,12). It is suggested that this apparent receptor upregulation may be due, in part, to concomitant redistribution of lymphocyte subsets, favoring an increase in T suppressor/cytotoxic and natural killer (NK) cells, which are known to have greater numbers of β_2-adrenoceptors (10,11,14). While a number of studies have demonstrated increases in these cell subtypes under stress (e.g., 1,13), it is unknown whether these changes covary with receptor upregulation when assessed under the same stimulus conditions.

The goals of the following study are twofold. First, we evaluate effects of acute stress on β_2 receptor density relative to measurements obtained among unstressed control subjects, and investigate whether any observed alterations in receptor density are associated with concomitant changes in circulating lymphocyte subpopulations. Second, we further examine the relationship of prestress receptor density to cardiovascular reactions induced by stress.

METHODS

Subjects

Thirty-three normotensive, undergraduate males (aged 18–22 years) were randomly assigned in a ratio of 2:1 to either a stress or control condition. In the stress condition, in vitro measure-

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ments of lymphocyte β-adrenoceptor density and cell subtype distributions were obtained before and immediately after subjects were administered a distinctly frustrating laboratory stressor. HR, blood pressure (BP), and plasma catecholamine (epinephrine and norepinephrine) concentrations were also assessed at baseline and during subjects' task performance. The same measurements were obtained in the control condition, 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 and caffeine for 12 h before attending a laboratory session beginning at 08:30 a.m. Upon arrival at the laboratory, subjects were seated in an upright position. A nurse inserted an intravenous catheter into a vein in the antecubital fossa of the subject's dominant arm. The catheter was connected to an exfusion pump via a short length of heparinized, SILASTIC tubing (Dow Corning, Midland, MI). Following venipuncture, an occluding cuff was placed on the subject's nondominant arm and connected to a vital signs monitor (Critikon Dinamap 8100) for automated measurement of HR (in beats per min (bpm), assessed during periods of cuff deflation) and systolic and diastolic BP (in mmHg). Each subject then rested for 30 min to achieve baseline conditions. During the last 6 min of this period, HR and BP (four readings) were recorded, and 30 ml of blood was drawn to determine baseline catecholamine concentrations, lymphocyte subtypes, and the density of β_2-adrenergic receptors on mononuclear leukocytes. At this point, control subjects were instructed to continue to sit quietly for 21 min, while the stress group performed a 21-min computerized version of the Stroop Color-Word Interference Test (4,18). Subjects indicated their responses by pressing one of four microswitches on a keypad with their dominant hand under pressure of time and against a distractor (randomized test responses) generated by computerized voice synthesis. HR and BP were recorded every 90 s; additional blood samples (total volume: 40 ml) were obtained in minutes 2, 11, and 20 of the task period for measurement of plasma catecholamines, and immediately on termination of the stressor for reevaluation of receptor density and lymphocyte subtypes. Blood samples were taken at corresponding times among unstressed controls.

Catecholamines

Blood samples were anticoagulated with ethylenediaminetetraacetic acid (EDTA), chilled, and immediately centrifuged at 4°C; plasma was then separated and frozen at −80°C until analysis. Epinephrine and norepinephrine were measured by high performance liquid chromatography (HPLC) with electrochemical detection (13). Following extraction with alumina, HPLC determinations were conducted using a Phase II, reverse phase, 3-micron column. Peak catechol heights were measured automatically by Chromatochart-PC and compared to standards tested for HPLC-EC purity (BAS/IMI).

Receptor Density

β_2-Adrenergic receptor density was determined on whole mononuclear leukocytes by saturation binding assay (modified from ref. 6). Cells were isolated on the same day as sampling using a modified version of the ficoll hypaque gradient method of Boyum (2). All steps were performed at 4°C in an attempt to suppress in vitro cell activity. Saturation binding isotherms were performed with $2-5 \times 10^5$ intact cells using [^{125}I]-iodopindolol (specific activity 2200 Ci/mmol (New England Nuclear Corp.)) at nine concentrations from 7.5 to 600 pM. Specific binding was defined as the difference between total binding and binding in the presence of 1 uM CGP-12177, a lipophobic ligand. Following an incubation period of 20 h at 4°C, the cells were harvested by rapid vacuum filtration over fiberglass receptor binding filters (Skatron 11734). Each filter was washed for 20 s with a solution of 50 mmol Tris HCL and 25 mmol magnesium chloride (4°C) and counted in a gamma counter. Binding affinities and B_{max} were derived from a weighted, nonlinear least squares estimate of binding parameters (LIGAND; 16). From these data receptor density was calculated, defined as the number of β_2-adrenergic receptors per cell (i.e., mononuclear leukocyte). To establish normality of distribution, these data were subjected to square root transformation, as recommended by Sokol and Rohlf (19) and Freeman and Tukey (5), prior to statistical analysis.

Lymphocyte Subtypes

Circulating populations of T-cell subtypes, B-cells, and NK cells were assessed in whole blood using flow cytometry. Lymphocyte subsets were analyzed using monoclonal antibodies labeled with either fluorescein or phycoerythrin to quantify CD3 (total T-cells), CD4 (T-helper cells), CD8 (T-suppressor/cytotoxic cells), CD19 (B-cells), and NK cells (13). The ratio of CD4 to CD8 cell numbers was calculated. Numbers of cells could not be computed for one experimental subject due to clotting.

RESULTS

Analyses were conducted to: (a) evaluate changes in HR, BP, catecholamine concentration, receptor density, and lymphocyte subtypes evoked by the Stroop task; (b) examine whether any alteration in receptor density was associated with a corresponding redistribution of lymphocyte subsets; and (c) in the experimental condition, determine whether the magnitude of change in HR and BP seen during task performance correlated significantly with individual differences in pretask receptor density or task-related catecholamine response.

Effect of Mental Stress on HR, BP, and Catecholamines

To evaluate effects of the Stroop test on cardiovascular and catecholamine measurements, repeated-measures ANOVAs were conducted on each dependent variable. For these analyses, HR and BP data were initially reduced by calculating a mean value for both baseline and experimental (task) periods (see Table 1); similarly, the three measures of epinephrine and norepinephrine concentration during the task period were averaged to yield a single value for each subject. Mean baseline and task values were used in the cardiovascular and catecholamine analyses because these values correlated highly with the individual readings from which the means were calculated. (Calculation of means is justified by the high average correlation between mean values and individual readings; for example, for experimental period measurements, epinephrine: $r = 0.86$; norepinephrine: $r = 0.95$.) Average correlations of the mean of each cardiovascular variable with its component values were: 0.95 and 0.96 for baseline and task HR; 0.91 and 0.88 for baseline and task SBP; 0.91 and 0.76 for baseline and task diastolic BP (DBP); 0.94 for task epinephrine; and 0.96 for task norepinephrine. Mean values were then subjected to 2×2 ($\text{Group}_{\text{experimental, control}}$) $\times$ ($\text{Period}_{\text{baseline, task}}$) repeated-measures ANOVAs. With the exception of plasma norepinephrine, each analysis revealed a significant Group $\times$ Period interaction: HR ($F(1, 31) = 16.98$, $p < 0.0004$), systolic and diastolic BP ([$F(1, 31) = 40.28$, $p < 0.0000$], [$F(1, 31) = 16.33$,

TABLE 1

MEAN CARDIOVASCULAR, PLASMA CATECHOLAMINE, LYMPHOCYTE SUBSET, AND RECEPTOR DENSITY DATA AT BASELINE AND TASK PERIODS AMONG STRESSED SUBJECTS AND UNSTRESSED CONTROLS (STANDARD DEVIATIONS IN PARENTHESES)

	HR bpm	SBP mmHg	DBP mmHg	Epi pg/ml	Norepi pg/ml	Receptors sites/cell	CD8 cells/mm^3	NK cells/mm^3	CD4/CD8 cell ratio	CD4 cells/mm^3	CD19 cells/mm^3	CD3 cells/mm^3
Experimental Group												
Baseline	65.5	124.40	66.8	39.9	224.8	479	505	166	1.51	747	234	1185
	(8.7)	(7.1)	(8.1)	(14.2)	(126.0)	(248)	(131)	(95)	(.33)	(220)	(78)	(296)
Task	73.3	135.8	73.7	45.4	247.3	551	582	269	1.29	727	227	1198
	(10.5)	(8.6)	(6.7)	(16.8)	(89.9)	(345)	(191)	(158)	(.32)	(245)	(73)	(362)
Control Group												
Baseline	63.8	123.0	63.0	37.6	246.9	316	527	112	1.50	740	251	1235
	(6.0)	(6.4)	(6.2)	(19.7)	(162.8)	(205)	(149)	(79)	(.47)	(107)	(92)	(199)
Task	64.4	121.8	62.4	35.8	244.9	404	526	131	1.42	707	257	1194
	(7.0)	(7.2)	(5.7)	(16.1)	(137.0)	(298)	(156)	(71)	(.37)	(109)	(98)	(236)

$p < 0.0004$], respectively), and plasma epinephrine ($F(1, 31) = 4.69$, $p < 0.03$). Subsequent comparisons among group means (by Dunn's procedure (18), $p < 0.05$) showed baseline measurements of experimental and control subjects to be comparable for all variables. Experimental subjects experienced a significant rise in HR, SBP, DBP, and plasma epinephrine concentration between the baseline and task periods, whereas values obtained at corresponding periods of measurement did not change among unstressed controls (see Table 1).

Effects of Mental Stress on Receptor Density and Lymphocyte Subsets

To determine the effect of mental stress on β_2-adrenoceptors, measures of receptor density were subjected to a 2 × 2 ($\text{Group}_{\text{experimental, control}}$) × ($\text{Period}_{\text{baseline, posttask}}$) repeated-measures ANOVA (untransformed values are presented in Table 1). This analysis revealed a significant Period main effect ($F(1, 31) = 4.74$, $p < 0.03$), reflecting an increase in the number of receptors/cell between baseline and posttask measurements across all subjects (untransformed $\bar{x}$'s = 464 (baseline) and 535 (posttask) receptors/cell). The absence of an expected Group × Period interaction ($F(1, 31) = 0.30$, $p < 0.59$) indicates that baseline-to-posttask change in receptor density did not differ between experimental and control groups.

Lymphocyte subsets were similarly analyzed by 2 × 2 (Group × Period) repeated-measures ANOVAs. Here, the Group × Period interaction term was significant on analysis of CD8 lymphocytes ($F(1, 30) = 7.43$, $p < 0.01$), NK cells ($F(1, 30) = 12.06$, $p < 0.002$), and the T-helper/suppressor ratio ($F(1, 30) = 12.58$, $p < 0.001$). Comparisons among means (by Dunn's procedure (18), $p < 0.05$) showed baseline measurements of experimental and control subjects to be comparable for all variables. As expected, experimental subjects experienced a significant rise in circulating numbers of CD8 and NK cells between the baseline and task periods, whereas values obtained at corresponding periods of measurement did not change among unstressed controls. Analysis of CD19 (B), CD4 (T-helper), and CD3 (Total T) lymphocyte subsets revealed no significant effects (see Table 1).

In sum, analysis of β_2-adrenoceptor density revealed a pre- to posttask increase in receptor numbers across all subjects; hence, receptor density did not rise differentially as a function of exposure to stress between the experimental and control conditions. In contrast, circulating CD8 and NK cells increased from pre- to posttask measurements, but did so only among experimental (stressed) subjects.

Baseline Receptor Density as a Predictor of Cardiovascular Response to Mental Stress

We next correlated the initial receptor density measurement (as well as task-related changes in plasma catecholamines) with cardiovascular responses to the Stroop task among subjects in the experimental condition. These correlations were calculated with respect to: (a) mean task responses, as averaged over the full 21-min task period; and (b) responses seen during the first 3 min of the Stroop task (in the case of catecholamines, the Minute 2 evaluation). The latter analyses were conducted to replicate observations made previously over a comparable interval by Mills et al. (15). To control for baseline covariation, residualized (i.e., baseline-adjusted) change scores for HR, BP, and plasma epinephrine and norepinephrine were employed in these analyses.

Pretask receptor density was associated positively with the magnitude of HR and SBP responses during the initial 3 min of the Stroop task (HR: $r = 0.57$, $p < 0.006$; SBP: $r = 0.48$, $p < 0.02$), but was not related significantly to mean responses recorded over the full task period (HR: $r = 0.31$, N.S.; SBP: $r = 0.25$, N.S.). Baseline receptor density was unrelated to task-related variability in DBP responses, either at 3 min or across the whole task. With respect to catecholamines, plasma epinephrine response at Minute 2 correlated marginally with the magnitude of HR acceleration during the initial 3 min of the Stroop task (HR: $r = 0.39$, $p < 0.08$), but was not related to initial BP responses (SBP: $r = 0.11$, N.S.; DBP: $r = 0.04$, N.S.). Similarly, mean plasma epinephrine response (i.e., across Minutes 2, 11, and 20) correlated positively with mean HR response ($r = 0.43$, $p < 0.04$), but was unrelated to mean BP responses (SBP: $r = 0.26$, N.S.; DBP: $r = 0.18$, N.S.). Plasma norepinephrine was unrelated to variability in cardiovascular responses, either at 3 min or over the whole task period (HR: $r = 0.07$ and 0.10; SBP: $r = 0.16$ and 0.21; DBP: $r = 0.03$ and 0.07 [at 3 min and over whole task, respectively]).

To determine whether relations between baseline receptor number and HR and BP responses in the first 3 min of the task were independent of changes in plasma catecholamines, partial correlations were calculated next, adjusting for concomitant changes in epinephrine. These analyses showed baseline receptor density to correlate marginally with HR change ($r = 0.35$, $p < 0.09$), whereas a significant relationship persisted with respect to change in SBP ($r = 0.56$, $p < 0.005$). To further illustrate these associations, we partitioned the distribution of baseline receptor measurements to identify clearly differentiated groups of subjects having a "high" or "low" density of lymphocytic adrenocep-

tors; these groups correspond to the upper and lower tertiles of the overall distribution of receptor measurements (untransformed binding sites/cell: Low (n = 7): X = 221; High (n = 8): X = 881). The arithmetic change in HR and SBP between baseline and task periods was then compared between High and Low receptor groups by analysis of covariance, with corresponding baseline measurement (for HR or SBP) and concomitant change in plasma epinephrine entered as covariates. As shown in Fig. 1, HR reactions to the Stroop task were not related significantly to receptor group after covariance adjustment for the epinephrine response ($F(1, 12) = 2.36, p = 0.15$). Consistent with results of the correlational analyses across all subjects, however, baseline receptor density did predict the initial systolic pressor response independently of concomitant changes in plasma epinephrine concentration ($F(1, 12) = 10.59, p < 0.007$).

DISCUSSION

The present study offers qualified support for previously reported associations between individual differences in β_2-adrenoceptor density and physiological response to mental stress (3,15). Consistent with Mills et al. (15), we observed that interindividual variability of pretask adrenergic receptor density covaried with HR reactivity in the first 3 min of the Stroop task (a period that also corresponds with the duration of stress employed in the Mills et al. study). Additionally, baseline receptor density covaried with subjects' systolic pressor responses over the same period. The latter finding corroborates an earlier report of heightened adrenoceptor density and sensitivity among persons exhibiting consistently large blood pressure responses to acute mental stress (17). That a similar relationship with respect to SBP was not observed by Mills et al. (15) may be attributable to the rather small pressor response evoked overall by the stimulus (mental arithmetic) administered in that study. Finally, a novel observation in this investigation is that the association between baseline β_2 receptor density and the initial SBP response to stress was independent of concomitant changes in plasma catecholamine concentrations.

It remains unclear why the same receptor-reactivity associations did not achieve significance when HR and BP measurements were averaged over the entire task period. Apparently, this was not due to a habituation of subjects' cardiovascular reactions over the course of the stressor, as responses recorded in the first 3 min were of about the same magnitude as those observed across the remainder of the task (i.e., Minutes 4–21) (HR Δ: 8.3 vs. 7.2 bpm; SBP Δ: 9.6 vs. 11.9 mmHg). One possible (albeit speculative) explanation for our findings is that different parameters of adrenergic function may variably influence cardiovascular reactions over time. For instance, receptor number may account for a significant proportion of the response variability seen immediately after stressor onset, with the increased release of catecholamines induced by stress accounting for a greater proportion of the variability observed thereafter. In this regard, it may be noted that baseline receptor density correlated significantly with subjects' SBP responses over the first 3 three min of the Stroop test ($r = 0.48, p < 0.05$), but that plasma epinephrine concentrations in the same interval did not ($r = 0.11$). Conversely, pretask receptor number was unrelated to subjects' systolic responses over the remaining task minutes (i.e., Minutes 4–21) ($r = 0.21$, N.S.), whereas the concurrent change in epinephrine was ($r = 0.42, p < 0.05$). Finally, we should acknowledge that receptor density and changes in the plasma concentration of catecholamines are only two indices of adrenergic activity that may sustain cardiovascular responses to mental stress. It is conceivable, therefore, that the measurement of other relevant factors, such as adrenoceptor sensitivity or second messenger release, would further enhance prediction of behaviorally elicited HR and BP reactivity.

Consistent with earlier reports (7,8), we found an acute increase in receptor density between baseline and posttask measurements, but this change was seen equally in experimental subjects and unstressed controls. Although interpretation of the parallel change in receptor density observed in the two groups is unclear, it is noteworthy that all previous studies showing a significant poststress rise in β_2 receptors failed to include an unstressed control condition (7,8,12). Hence, our data do not support the hypothesis that brief mental stress induces an acute

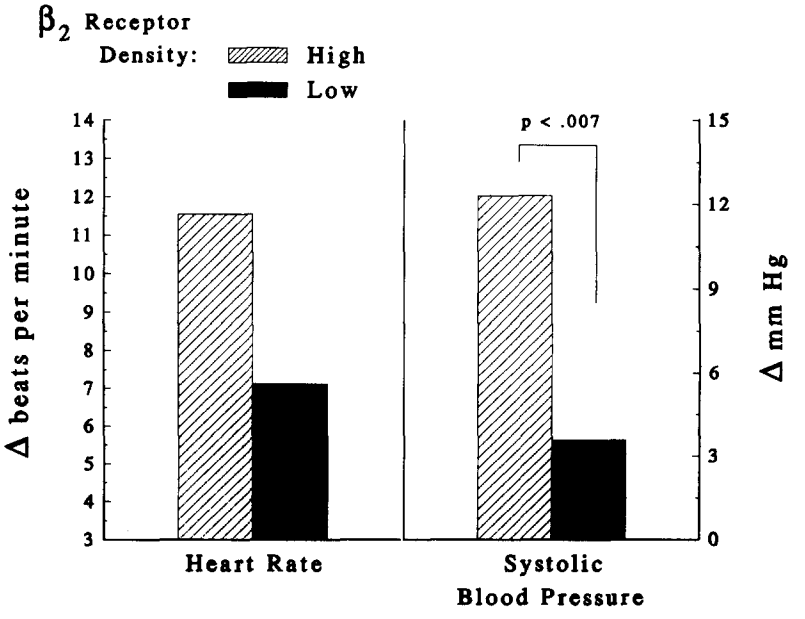

FIG. 1. Heart rate and systolic blood pressure reactions of High and Low receptor groups after covariance adjustment for change in epinephrine.

increase in β_2 receptor density. Although it is possible that the increase in receptor number between baseline and posttask values reflects normal variation due to time of day, we are aware of no evidence that receptor densities in man show a marked diurnal cyclicity, and in any case, the interval between measurements obtained here was only 20 min. A second possibility is that we are observing a delayed response to the stress of venipuncture—a response common to both the experimental and control conditions and apparent after 50 min, but not detectable at the time of baseline assessment. In this case, any additional change in receptor number attributable to the Stroop test might be expected to occur only at some point later than the terminal measurement obtained here. Whatever the reason for the present outcome, it remains that we observed no differential reactivity to stress in the experimental and control conditions of this experiment, and that in the absence of comparably treated control subjects in previous experiments, it cannot yet be concluded that mental stress, at least of the type and magnitude employed here and in previously reported studies, evokes a reliable change in β_2-adrenoceptor density.

Unlike receptor number, CD8 and NK cell numbers increased selectively among subjects assigned to the experimental condition. These results add to a growing body of evidence that cellular immune function can be altered by acute psychological stress (1,9). Insofar as lymphocyte redistribution differed by group and therefore did not parallel the increase in receptor numbers seen in both experimental and control subjects, our findings do not support the hypothesis that stress-related increases in receptor density are due to expanded numbers of cell subtypes bearing higher numbers of receptors, notably CD8 and NK cells (10,11,14). The lack of an association between lymphocyte subset distribution and receptor density is underscored by the further observation that even among experimental subjects, for whom both receptor number and lymphocyte subsets increased following stress, the magnitude of change in these parameters did not covary (Δ_{CD8}: $\Delta_{receptors}$: $r = 0.35$; N.S; Δ_{NK}: $\Delta_{receptors}$: $r = 0.28$; N.S.; $\Delta_{CD4/CD8}$: $\Delta_{receptors}$: $r = 0.18$; N.S.). While it is possible that a more provocative stressor may have induced parallel changes in receptor density and lymphocyte subset redistribution, further research is needed to establish that receptor numbers, as measured on lymphocytes, increase with exposure to acute stress, and that such changes are attributable to a concomitant redistribution of those lymphocyte subsets that have a greater density of adrenergic receptors.

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