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MOOD STATES, SYMPATHETIC ACTIVITY, AND IN VIVO β -ADRENERGIC RECEPTOR FUNCTION IN A NORMAL POPULATION

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Abstract

The purpose of this study was to examine the relationship between mood states and β -adrenergic receptor function in a normal population. We also examined if sympathetic nervous system activity is related to mood states or β -adrenergic receptor function. Sixty-two participants aged 25–50 years were enrolled in this study. Mood states were assessed using the Profile of Mood States (POMS). β -adrenergic receptor function was determined using the chronotropic 25 dose isoproterenol infusion test. Level of sympathetic nervous system activity was estimated from 24-hr urine norepinephrine excretion. Higher tension-anxiety, depression-dejection, and anger-hostility were related to decreased β -adrenergic receptor sensitivity (i.e., higher chronotropic 25 dose values), but tension-anxiety was the only remaining independent predictor of β -adrenergic receptor function after controlling for age, gender, ethnicity, and body mass index (BMI). Urinary norepinephrine excretion was unrelated to either mood states or β -adrenergic receptor function. These findings replicate previous reports that anxiety is related to decreased (i.e., desensitized) β -adrenergic receptor sensitivity, even after controlling for age, gender, ethnicity, and body mass index.

Keywords

mood state; β -adrenergic receptor function; norepinephrine; sympathetic nervous system

INTRODUCTION

Many researchers have been interested in the relationship between mood states and human adrenergic receptor physiology. For example, anxiety is well known to have a close relationship with sympathetic nervous system (SNS) activity [Yager and Gitlin, 2000]. Some studies also suggest that patients with anxiety disorders show dysregulation of the noradrenergic system [Charney et al., 1992; Kim et al., 2004; McCraty et al., 2001; Sevy et al., 1989]. Abnormalities of SNS activity are noted in many medical conditions such as ischemic heart disease and congestive heart failure [Hadase et al., 2004; Kaye et al., 1995; Lambert et al., 1995; Petersson et al., 2005; Schomig et al., 1984] as well as in psychiatric disorders.

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Reduced β -adrenergic receptor function has been largely addressed in terms of reduced receptor density ($B_{\max}$) or sensitivity (cyclic adenosine monophosphate production to isoproterenol) on circulating lymphocytes. Stress, hostility, and tension-anxiety have been shown to be associated with lymphocyte β -adrenergic receptor down-regulation in healthy people [Dimsdale et al., 1994; Mills et al., 1997; Suarez et al., 1997; Yu et al., 1999]. There are limitations, however, to using the lymphocyte β_2 -adrenergic receptor as an index of end-organ β -adrenergic receptor function: the distribution of lymphocyte subsets is influenced by acute and chronic stress and this can undermine the validity of this lymphocyte β_2 -adrenergic receptor model [Mills and Dimsdale, 1993].

In three recent studies using the in vivo chronotropic 25 dose (CD_{25}) method of determining β -receptor responsiveness, hostility was related to reduced β -adrenergic receptor sensitivity [Hughes et al., 2003; Jain et al., 2004; Sherwood et al., 2004]. CD_{25} is an in vivo technique for assessing β -adrenergic receptor function where the change in heart rate in response to incremental doses of isoproterenol provides an index of cardiac β -adrenergic receptor sensitivity [Cleaveland et al., 1972]. CD_{25} is defined as the dose of isoproterenol necessary to increase heart rate by 25 beats/min. CD_{25} provides a more direct assessment of cardiac β -adrenergic receptors than lymphocyte β_2 -adrenergic receptors. CD_{25} is known to be inversely related to lymphocyte β -adrenergic receptor sensitivity and is a stable and reliable indicator of cardiac sensitivity to isoproterenol [Mills and Dimsdale, 1993].

The processes by which β -adrenergic receptor down-regulation is related to emotional factors—especially anxiety or tension—in humans is unclear. Recently, there was a report that anxiety level was positively correlated with β -adrenergic receptor function in a normal healthy population [Kang and Yu, 2005]. Thus, normative information on the relationship between various mood states and β -adrenergic receptor function in non-psychiatric populations is still in question.

In a normal population, this study examined the relationship between mood states and β -adrenergic receptor function as assessed by the in vivo CD_{25} test. We also examined if urinary norepinephrine (NE) levels were related to the psychological variables and to β -adrenergic receptor function.

METHODS

PARTICIPANTS

The sample consisted of 62 participants with 23 women (11 African Americans and 12 Caucasian Americans) and 39 men (14 African Americans and 25 Caucasian Americans), aged 25–50 years ($M = 37.2$, $SD = 7.6$). Sample characteristics are listed in Table 1. Participants were recruited by local advertisements and referrals. Individuals with major medical or psychiatric problems were excluded from the study. Thus, those with a history or current evidence of heart disease, liver or renal disease, diabetes, mood disorders, psychosis, severe asthma, cerebrovascular disease or cancer, current drug or alcohol abuse, creatinine levels ≥ 1.4 mg/dl, renal bruit on physical examination, systolic blood pressure >180 mmHg or diastolic blood pressure >90 mmHg, fasting glucose >120 mg/dl, and known sleep disorders were excluded. Perimenopausal women and those taking hormone replacement therapy or oral contraceptives were excluded. The study was approved by the University of California, San Diego (UCSD) Institutional Review Board. After informed written consent was given, participants were studied at the UCSD General Clinical Research Center (GCRC).

PSYCHOLOGICAL MEASURES

Several dimensions of mood states were assessed using the Profile of Mood States [POMS; McNair et al., 1992], a 65-item self-administered rating scale which measures six dimensions of mood (tension-anxiety, depression-dejection, fatigue-inertia, confusion-bewilderment, vigor-activity, and anger-hostility).

ISOPROTERENOL STIMULATION TEST AND CD₂₅

The standardized isoproterenol stimulation test and calculation of CD₂₅ was performed as described previously [Cleaveland et al., 1972]. After a history and physical examination, participants were connected to an electrocardiogram monitor to measure heart rate. Following a 30-min rest, basal heart rate was determined. Participants were first given an intravenous low-dose bolus (0.1 µg) of isoproterenol, and then infused with incremental bolus doses of isoproterenol (0.25, 0.5, 1.0, 2.0, 4.0 µg) until an increase of heart rate greater than 25 beats/min above basal heart rate was observed or after the 4.0 µg bolus was completed. Maximum heart rate after each injection was calculated as the mean of the three shortest R-R intervals. There was a time interval of at least 5 min between each dose.

24-HR URINE NOREPINEPHRINE MEASUREMENT

Participants collected urine over a 24-hr period during an overnight stay at the GCRC. Samples were obtained at two collection intervals (one from 10 PM to 6 AM and the other 6 AM to 10 PM) and stored at -80°C until they were assayed. NE level was measured by radio-enzymatic assay according to the method described by Kennedy and Ziegler [1990]. Urine NE levels (NE₂₄) were adjusted for urine volume excreted over time. NE values >3 SD from the mean were discarded; one woman with extreme values was thus excluded from the analysis.

STATISTICAL ANALYSES

Simultaneous and hierarchical multiple linear regression analyses were used. Univariate analyses were conducted via regression to examine whether the variables of age, gender, ethnicity, body mass index (BMI), and mood states were significant predictors of CD₂₅. Hierarchical multiple regression analyses were used to examine whether anxiety, depression, or hostility on POMS scales could predict CD₂₅ after controlling for age, gender, ethnicity, and BMI. Pearson correlation analyses were performed to evaluate the relationship among NE₂₄, psychological variables, and CD₂₅ values. Categorical variables were dummy coded. Analyses were run on the SPSS version 12.0 software. The criterion for statistical significance was set at $P < .05$.

RESULTS

Age was related to CD₂₅ ($F[1, 60] = 5.78, P = 0.019$) compatible with decreased β-adrenergic receptor function with aging. Among the psychological variables, POMS tension-anxiety ($F[1, 60] = 7.14, P = 0.01$), depression-dejection ($F[1, 60] = 5.35, P = 0.024$), and anger-hostility ($F[1, 60] = 7.22, P = 0.009$) were all significantly related to CD₂₅.

Secondary analyses were performed to determine whether the POMS subscales would be related to CD₂₅ after controlling for age, gender, ethnicity, and BMI (Table 2). Age, gender, ethnicity, and BMI were entered on step 1. This model significantly accounted for variance of CD₂₅ ($F[4, 54] = 3.10, p = 0.024, R^2 = 0.185$), and gender was the only significant predictor of CD₂₅ (males: 5.76 ± 2.19 versus females: 4.12 ± 2.22 , respectively, $P < 0.05$). In step 2, POMS tension-anxiety, depression-dejection, and anger-hostility were entered separately. Neither POMS depression-dejection nor anger-hostility was found to be independent predictors of

CD₂₅ after controlling for age, ethnicity, gender, and BMI. In contrast, tension-anxiety continued to be related to CD₂₅, even after controlling for age, ethnicity, gender, and BMI.

NE₂₄ was neither related to CD₂₅ nor any subscales of the POMS (all *P* values >0.2).

DISCUSSION

We examined the relationship among β -adrenergic receptor sensitivity, 24-hr urine NE level and mood in a normal population. Our study supports previous findings that some negative mood states are associated with decreased β -adrenergic receptor function. In addition, to the best of our knowledge, this study was the first to include urinary NE excretion for examination of the relationship between tension-anxiety and in vivo β -adrenergic receptor responsiveness. Tension-anxiety rather than anger-hostility or depression-dejection was the only independent predictor of β -adrenergic receptor function after controlling for confounding variables such as age, gender, ethnicity, and BMI.

Decreased β -adrenergic receptor responsiveness is reported in anxiety disorders or depression [Maddock et al., 1993; Mazzola-Pomietto et al., 1994; Pandey et al., 1987], whereas little is known in a normal population. Hostility has also been reported to be associated with decreased β -adrenergic receptor responsiveness [Hughes et al., 2003; Sherwood et al., 2004; Suarez et al., 1997]. Tension and anxiety have been posited as risk factors for the development of ischemic heart disease and cardiovascular mortality [Albert et al., 2005; Eaker et al., 2005; Kawachi et al., 1994], perhaps via activation of noradrenergic system and desensitization of cardiac β -adrenergic receptors [Iyer and Canty, 2005; Lambert et al., 1995; Leineweber et al., 2005; Schomig et al., 1984]. Our study using an in vivo technique demonstrated a relationship between mood state and β -adrenergic receptor function in healthy persons. CD₂₅ provides the advantages of determining the cardiac β_1 - and β_2 -adrenergic receptor responsiveness more directly than measuring lymphocyte β_2 -adrenergic receptors in vitro [Cleaveland et al., 1972; Mills and Dimsdale, 1993].

It is interesting and challenging to reconcile our observations in normals with the observations in panic disorder (PD) patients. A host of superb studies in PD patients have demonstrated autonomic abnormalities. For instance, isoproterenol can act as a panicogen, which suggests a hypersensitivity to isoproterenol in PD [Pohl et al., 1988]. The cardiovascular hyperreactivity in PD is closely related to abnormalities of neurotransmitter and neuroendocrine responses including noradrenergic system [Boulenger et al., 1984; Gorman et al., 2000; Uhde et al., 1986, 1992] as well as β -adrenergic receptors. In addition, enhanced cardiac sympathetic activity has been inferred from altered heart rate variability or QT variability in PD patients [Pohl and Yeragani, 2001; Yeragani et al., 1993, 1995, 2000]. Desensitization of β -adrenergic receptors is thought to be induced by increased SNS activity [Aarons et al., 1983; Tsujimoto et al., 1984]. Thus, our result in a normal population extends some of the previous findings in PD patients.

Only one previous study suggested that urinary NE predicted CD₂₅ [Sherwood et al., 2004]. In our study, NE₂₄ was neither related to CD₂₅ nor negative moods (Fig. 1). This lack of association may reflect the complexities of synaptic processes determining a catecholamine level [Esler et al., 1990].

There are several limitations in this study. First, we did not perform a structured psychiatric interview to assess the subjects in this study, and thus we cannot completely exclude the possibility that some subjects might have had a psychiatric illness such as clinical depression or anxiety disorders. Second, there is a possibility that test anxiety during the isoproterenol stimulation test could have affected the study results, although we did all laboratory tests in a comfortable GCRC facility with laboratory personnel who were familiar with the subjects to

reduce test anxiety. Third, although CD₂₅ measures in vivo state of peripheral β -adrenergic receptors, it is not clear yet how exactly the peripheral measures mirror the brain adrenergic receptor activity. In addition, our sample size is relatively small to extend our hypothesis to a general population. In conclusion, using a sensitive in vivo measure of β -adrenergic receptor sensitivity, our findings suggest that tension-anxiety is related to reduced (i.e., desensitized) β -adrenergic receptor function in a normal population.

CONCLUSION

In this study, anxiety was associated with decreased β -adrenergic receptor sensitivity in a normal population even after controlling some confounding variables. Although we did not observe a positive finding about the relationship between urine NE level and β -adrenergic receptor sensitivity, further investigation including SNS activity will be needed to understand the relationship between mood states, β -adrenergic receptor function, and cardiovascular risk.

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Figure 1.
Result of a linear regression between 24-hr urine norepinephrine and chronotropic 25 dose.
There was no significant relationship between them ($R = 0.148$, $R^2 = 0.022$, $P = 0.278$).

TABLE 1

Sample characteristics

Variable	Mean±SD
<i>N</i>	62
Ethnicity	
White	37
Black	25
Age (years)	37.2±7.6
BMI (kg/m ²)	26.5±5.3
POMS scales	
Tension-anxiety	5.4±3.7
Depression-dejection	4.3±5.5
Fatigue-inertia	4.8±4.2
Confusion-bewilderment	3.3±3.1
Vigor-activity	13.0±5.5
Anger-hostility	4.0±4.4
CD ₂₅ (µg isoproterenol)	5.17±2.32
NE ₂₄ (ng/h) ^a	34.9±26.1

BMI, body mass index; POMS, Profile of Mood States; CD₂₅, chronotropic 25 dose; NE₂₄, urinary norepinephrine excretion over time.

^aData were available for *n* = 56.

TABLE 2
Hierarchical multiple linear regression analyses predicting CD₂₅

Variable	β	P	R ²	F	P
Step I: initial model			0.185	3.068	0.024
Age	0.134	0.331			
Ethnicity	-0.009	0.947			
Gender	-0.348	0.010			
BMI	0.195	0.132			
Step II: Model 1 tension-anxiety			0.259	3.707	0.006
Age	0.052	0.701			
Ethnicity	-0.023	0.858			
Gender	-0.315	0.015			
BMI	0.109	0.398			
POMS tension-anxiety	0.305	0.025			
Step II: Model 2 depression-dejection			0.229	3.154	0.014
Age	0.107	0.429			
Ethnicity	-0.307	0.780			
Gender	-0.310	0.020			
BMI	0.124	0.348			
POMS depression-dejection	0.231	0.087			
Step II: Model 3 anger-hostility			0.231	3.184	0.014
Age	0.119	0.378			
Ethnicity	-0.011	0.932			
Gender	-0.301	0.024			
BMI	0.109	0.420			
POMS anger-hostility	0.235	0.081			

BMI, body mass index; POMS, Profile of Mood States; CD₂₅, chronotropic 25 dose.