
Adrenergic Status in Anxiety Disorders: Platelet Alpha₂-Adrenergic Receptor Binding, Blood Pressure, Pulse, and Plasma Catecholamines in Panic and Generalized Anxiety Disorder Patients and in Normal Subjects

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In order to evaluate adrenergic function in anxiety disorders, platelet alpha₂-adrenergic binding parameters and supine and standing blood pressure, pulse, and venous plasma epinephrine and norepinephrine were determined in patients with panic attacks or generalized anxiety disorder and in normal subjects. The maximum number of binding sites (B_{max}) for the partial agonist tritiated clonidine was significantly lower for both patient groups than for normal subjects, and the B_{max} for the antagonist tritiated yohimbine was significantly lower for panic patients. There were no other substantive differences across groups. Prior exposure to psychotropic drugs might account for the results for clonidine binding, but not for yohimbine. The B_{max} for clonidine was correlated with norepinephrine increases upon standing and, for panic patients, with the severity of full unexpected panic attacks. These data provide further evidence of adrenergic receptor abnormalities in people with anxiety disorders.

Introduction

Symptoms and physiological changes potentially associated with adrenergic dysfunction have been reported in people with anxiety disorders (Redmond 1979; Gorman 1984; Ursano 1985; Cameron and Nesse 1988; Hoehn-Saric and McLeod 1988). Reported physiological changes include abnormalities of blood pressure (Nesse et al. 1985b; Mathew and Wilson 1986; White and Baker 1986; Charney et al. 1984, 1987; Balon et al. 1988; Cameron and Nesse 1988; Gorman et al. 1988a), pulse (Freedman et al. 1984;

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Taylor et al. 1986; Shear et al. 1987; Baion et al. 1988; Cameron and Nesse 1988; Gorman et al. 1988a; Gorman et al. 1989), plasma (Mathew et al. 1981; Ballenger et al. 1984; Cameron et al. 1984; Nesse et al. 1984, 1985b; Villacres et al. 1987; Cameron and Nesse 1988; Gorman et al. 1988a; Sevy et al. 1989), and urinary (Nesse et al. 1985a; Kosten et al. 1987) catecholamines, and the catecholamine metabolite MHPG (3-methoxy-4-hydroxyphenylglycol) (Ko et al. 1983; Sheehan et al. 1983; Charney et al. 1984, 1987; Sevy et al. 1989). However, in several studies significant abnormalities of these variables have not been observed (Charney et al. 1985; Liebowitz et al. 1985; Carr et al. 1986; Cameron et al. 1987b; Edlund et al. 1987; Margraf et al. 1987; Pohl et al. 1987; Schneider et al. 1987; Cameron and Nesse 1988; Castellani et al. 1988; Crow et al. 1988; Curtis and Glitz 1988; Uhde et al. 1988; Woods et al. 1987, 1988a; Gorman et al. 1989). Abnormalities, when observed, sometimes have been in basal levels, but sometimes only in response to challenge testing. The inconsistencies in these results might be due, at least in part, to the fact that the physiological difference between anxious individuals and normal subjects may lie not in these variables per se, but rather in their regulation. Adrenergic receptors play a fundamental role in regulation of adrenergic functioning.

Adrenergic receptor abnormalities have been reported in people with anxiety disorders. Central nervous system (CNS) beta-adrenergic receptors do not appear to be functionally abnormal; beta-adrenergic blocking agents do not reliably decrease the psychological symptoms of anxiety (Cole 1984; Noyes 1985). However, peripheral beta-adrenergic receptor function appears to demonstrate subsensitivity, as indicated by a reduced in vitro lymphocyte cyclic AMP (cAMP) response (Lima and Turner 1983; Charney et al. 1989a) and a diminished heart rate response to isoproterenol in panic patients (Nesse et al. 1984); lymphocyte beta-adrenergic receptor number has been reported to be either decreased (Brown et al. 1983; Aronson et al. 1989) or increased (Albus et al. 1986). Thus, the bulk of the research indicates normal CNS beta-adrenergic receptor status but peripheral beta-adrenergic receptor down-regulation in anxious people. Lymphocyte beta-adrenergic receptors are also decreased in depressed individuals (Extein et al. 1979; Pandey et al. 1979; Mann et al. 1985; Wood et al. 1986; Carstens et al. 1987; Magliozzi et al. 1989); one study has suggested that anxiety is a factor in this decrease (Magliozzi et al. 1989).

Alpha₂-adrenergic receptor function has also been evaluated in people with anxiety disorders. CNS alpha₂-adrenergic receptors have been evaluated by administration of centrally active pharmacological agents. The growth hormone response to the alpha₂-adrenergic receptor partial agonist clonidine was blunted in panic patients in all but one of the reported studies (Charney and Heninger 1986; Uhde et al. 1986, 1989; Schittecate et al. 1988; Curtis et al. 1989; Nutt 1989), suggesting receptor subsensitivity; however, the cortisol response to clonidine did not demonstrate any abnormality (Stein and Uhde 1988). Clonidine administration also produced abnormalities of MHPG and diastolic blood pressure in panic patients in one study (Charney and Heninger 1986), but no abnormality of blood pressure in another (Uhde et al. 1989). Administration of yohimbine, an alpha₂-adrenergic receptor antagonist, to panic patients demonstrated abnormalities of systolic blood pressure and MHPG (Charney et al. 1984), as well as differences in pattern of cerebral blood flow (Woods et al. 1988b); patients with generalized anxiety disorder (GAD) had responses more like normal subjects (Charney et al. 1989b). Depressed individuals demonstrate a similar growth hormone response to clonidine as panic patients (Matussek et al. 1980; Checkley et al. 1981; Charney et al. 1982; Siever and Uhde 1984; Nutt and Cowan 1987; Amsterdam et al. 1989). In response to yohimbine, increases in MHPG and symptom ratings were smaller in depressed than in panic patients (Heninger et al. 1988).

Alpha₂-adrenergic receptors in the periphery have also been evaluated in anxious patients. In addition to measures such as blood pressure, which are likely to reflect both CNS and peripheral mechanisms, the status of the platelet alpha₂-adrenergic receptor in anxious patients has been evaluated. The platelet alpha₂-adrenergic receptor is of particular interest because (1) the presynaptic alpha₂-adrenergic receptor has been implicated at several levels in the control of adrenergic nervous system functioning (Langer 1980; Starke 1981; Dubacovitch 1984; U'Pritchard 1984), and (2) the platelet appears to provide a model of the monoaminergic neuron (Abrams and Solomon 1969; Stahl 1977; Campbell 1981) although others have questioned this relationship (Hamilton et al. 1985; Hamilton and Reid 1986; Nutt 1987). The binding of tritiated dihydroergocryptine, a nonselective alpha-adrenergic antagonist, is increased in panic patients (Roy-Byrne and Uhde 1985). Two studies (Cameron et al. 1984; Albus et al. 1986) that used the antagonist ligand tritiated yohimbine reported a decreased number of platelet receptors in panic patients, and two studies that used yohimbine (Nutt and Fraser 1987; Charney et al. 1989a), one using tritiated clonidine (Cameron et al. 1984), and one using the antagonist tritiated rauwolscine (Norman et al. 1987) did not find a difference. Patients with GAD also appear to have decreased tritiated yohimbine binding (Sevy et al. 1989), and patients with posttraumatic stress disorder had decreased rauwolscine binding (Perry et al. 1987). Platelets from depressed patients appear to show *increased* agonist binding but normal antagonist binding (Garcia-Sevilla et al. 1981b; Cameron et al. 1984; Katona et al. 1987; Sevy et al. 1989), although patients with both panic disorder and major depression appear to have binding similar to panic patients (Grunhaus 1988; Grunhaus et al. in press).

There are important relationships among adrenergic receptors, circulating catecholamine levels, and blood pressure and pulse. Both heart action and vascular tone are influenced by both alpha and beta receptors (Lees 1981; Mills and Dimsdale 1988). It has been well documented that there is an association of levels of circulating catecholamines with pulse and blood pressure (Cryer 1980; Ziegler and Lake 1984; Weiner 1985). Exposure to beta-adrenergic agonists decreases beta-adrenergic receptors whereas exposure to antagonists produces an increase in lymphocytes (Galant et al. 1978; Fraser et al. 1981; Aarons et al. 1982, 1983; Krause et al. 1988) and other tissues (Aarons et al. 1982; Snively et al. 1983, 1985; Pecquery et al. 1984; Tsujimoto et al. 1984); additionally, there was a positive correlation between lymphocyte beta-adrenergic receptor status with cardiac and lung beta-adrenergic receptor number (Aarons et al. 1982; Brodde et al. 1986) and cardiac isoproterenol sensitivity (Fraser et al. 1981).

The relationship of alpha₂-adrenergic receptors with blood pressure, pulse, and circulating catecholamines has also been studied. Some studies have indicated that alpha₂-adrenergic receptors are influenced by circulating catecholamine levels (Davies et al. 1981, 1982; Holliester et al. 1983; Siever et al. 1983; Cameron et al. 1984; Egan et al. 1985; Krause et al. 1988; Sevy et al. 1989) but other studies did not observe any effect (Baker and Drew 1981; Motulsky et al. 1983; Snively et al. 1983, 1985; Pecquery et al. 1984; Pfeifer et al. 1984). One study has questioned "the importance of peripheral alpha₂-receptors in the regulation of norepinephrine release in man" (FitzGerald et al. 1981). Finally, several studies have indicated that antidepressant drugs down-regulate both beta and alpha₂-adrenergic receptors (Smith et al. 1981; Cohen et al. 1982; Racagni et al. 1983; Janowsky and Sulser 1987). The mechanism by which this down-regulation occurs is unknown; it might relate to changes in synaptic norepinephrine levels.

In our own prior study (Cameron et al. 1984), we reported that the maximum number of platelet binding sites (B_{max}) as measured by the antagonist tritiated yohimbine was lower in panic patients than in normal subjects, but that binding of the partial agonist

tritiated clonidine was normal. Pretreatment plasma catecholamines were slightly higher in panic patients, and increased significantly during treatment with imipramine; imipramine treatment produced decreases in binding of both ligands. The clonidine B_{max} was negatively correlated with the magnitudes of the epinephrine and norepinephrine increases; the yohimbine B_{max} was negatively correlated with the increase in dopamine. The objectives of the present study were (1) an attempt to replicate our prior platelet α_2 -adrenergic receptor findings with panic patients versus normal subjects; (2) study of an additional group of patients with GAD; (3) comparison of supine and standing circulating catecholamines, blood pressure, and pulse in these three groups; (4) determination of the relative frequency of mitral valve prolapse (MVP) in the two patient groups; (5) evaluation of the correlations between receptor binding and the other adrenergic markers variables, as well as evaluation of the potential effects of prior psychotropic drug treatment on receptor binding; and (6) determination of the relationship between adrenergic marker variables and anxiety symptoms.

Methods

Subjects

Patients with panic disorder or agoraphobia with panic attacks, or GAD, and normal subjects were studied; all were drug free for at least 10 days before the start of the study. All patients were diagnosed by DSM-III criteria (Task Force on Nomenclature and Statistics, 1980) with the SCID-UP (Upjohn version of the Structured Clinical Interview for DSM-III, Spitzer and Williams 1983, 1988) administered by a clinician experienced in the evaluation of people with anxiety. All patients were experiencing symptoms severe enough to qualify for the respective diagnoses at the time of initiation of the study, including the occurrence of at least one panic attack per week for the previous 3 weeks in the panic patients. None reached criteria for any affective disorder diagnosis. No normal subject reached criteria for any DSM-III Axis I diagnosis, based on research diagnostic criteria (Spitzer et al. 1978) as determined by the Schedule for Affective Disorders and Schizophrenia-Lifetime (SADS-L) (Spitzer and Endicott 1985), Structured Clinical Interview for DSM-III (SCID-UP) (Spitzer and Williams 1983, 1988), or a semistructured clinical interview administered by an experienced clinician; no patient or normal subject had any known medical illness other than MVP in some of the patients. Symptom severity was determined at the time of study with the Panic Attack and Anticipatory Anxiety Scale (Sheehan 1986). Patients in both groups and normal subjects were studied concurrently. All subjects gave written informed consent.

Procedure

All subjects were studied between 7:30 AM and 10:30 AM. Upon arrival in the laboratory, each subject assumed a supine position and had a 19-gauge catheter inserted in an antecubital vein which was used for all blood sampling. After 20 min supine, a 70-ml blood specimen was withdrawn. From this specimen platelets were isolated for determination of membrane α_2 -adrenergic receptor binding and plasma was used to determine levels of the catecholamines epinephrine and norepinephrine. After 30 min supine, a 10-ml blood specimen was obtained for another determination of catecholamine levels. After this specimen was obtained, each subject stood for 15 min, after which another

10-ml blood specimen for catecholamines was obtained. Blood pressure and pulse were measured in the opposite arm immediately before each blood specimen was obtained. Seventeen of the 24 panic patients and all 8 of the GAD patients had evaluations for MVP; normal subjects were not evaluated for MVP.

Platelet membrane α_2 -adrenergic receptor binding assays were performed by our previously published method (Garcia-Sevilla et al. 1981a; Cameron et al. 1984). Receptor binding assays were always performed on the day on which the platelets were obtained; platelet membranes were never frozen. Specific binding of tritiated clonidine, a specific partial agonist for the platelet α_2 -adrenergic receptor, and tritiated yohimbine, a specific antagonist, were determined. Specific binding was approximately 85% for tritiated clonidine and approximately 90% for tritiated yohimbine. Estimates of the B_{max} and apparent dissociation constant (K_D) were made by using a nonlinear regression computer program (Munson and Rodbard 1980). Plasma for epinephrine and norepinephrine determinations was stored at -80°C until assay. Catecholamines were determined by the radioenzymatic technique. MVP evaluations were completed on a separate day; MVP was determined according to our previously described criteria (Nesse et al. 1985a).

Data Analysis

Four types of statistical analyses were performed. First, univariate analyses of variance (ANOVA) and regression analyses were used to compare group means across the three diagnostic groups for the binding parameters, blood pressure, pulse, and plasma catecholamines. Post hoc Scheffe' tests were used when the overall ANOVA F-ratio was significant. Correlation coefficients and *t*-tests were used to determine if age, gender, or drug-free duration prior to study affected the results. Second, a chi-square analysis was used to determine if the percentage of panic patients with MVP differed from the percentage of GAD patients with MVP. Third, in order to determine the relationship between platelet α_2 -adrenergic receptor binding status and the other physiological variables, correlations were determined for each of the four binding parameters (both B_{max} and K_D for tritiated clonidine and for tritiated yohimbine) with each other and with the other variables, separately for the three diagnostic groups, and for combined subject groups.

The fourth type of analysis involved correlations of symptom variables with the four binding variables for panic patients. The symptom variables included number of panic attacks, average duration of each attack, and average severity of each attack in the past week; percentage of time during the past week during which the patient was anxious about the occurrence of an attack and the average severity of that anxiety ("anticipatory anxiety") was also rated (Sheehan 1986). Correlations were performed for each of the symptom variables, and also for the "total severity scores." Total severity scores were used as a more global estimate of anxiety severity; they were calculated as number of attacks \times average duration \times average intensity. A total score for anticipatory anxiety was calculated as average intensity \times percentage of time experiencing anxiety. Because of lack of normality of data distribution, data were log transformed: $\log(1 + x)$. Binding parameters were correlated with total severity scores for full situational attacks, limited situational attacks, full unexpected attacks, limited unexpected attacks, and anticipatory anxiety. Full attacks involve three or more panic attack symptoms, and limited attacks involve one or two symptoms. Situational attacks involve an apparent precipitant, whereas unexpected attacks do not. For all four types of analyses,

Table 1. Means (Standard Deviations) and Numbers of Subjects in the Three Groups

Variable	Panic patients	Generalized anxiety patients	Normal subjects
Cl B_{max}	24.9(11.5)22	22.8(6.3)7	32.5(7.1)31
Cl K_D	5.10(2.61)22	2.81(1.18)7	5.86(2.42)31
Y B_{max}	108(33)23	114(40)7	134(34)31
Y K_D	3.34(1.18)23	2.93(1.29)7	3.06(1.39)31
NE1	216(76)16	174(40)8	189(68)10
NE2	223(76)15	210(51)8	218(98)10
NE3	479(167)15	464(107)8	491(169)9
E1	43(34)14	33(25)7	25(24)9
E2	39(33)14	45(28)8	35(43)8
E3	57(49)13	69(46)8	37(31)9
P1	67(11)19	65(9)8	67(8)12
P2	66(10)18	66(8)8	65(9)12
P3	83(14)18	84(12)8	77(9)11
SBP1	106(13)8	103(9)8	107(9)12
SBP2	106(12)18	104(16)8	106(8)12
SBP3	111(11)18	98(18)8	111(11)12
DBP1	65(11)18	67(5)8	67(7)12
DBP2	66(12)18	64(6)8	65(10)12
DBP3	78(12)18	71(15)8	78(7)12

Cl: tritiated clonidine (a partial α_2 -adrenergic receptor agonist for the platelet receptor), Y: tritiated yohimbine (a platelet α_2 -adrenergic receptor antagonist), B_{max} : maximum number of binding sites (femtomol/mg protein), K_D : apparent dissociation constant (nm), NE: norepinephrine (pg/ml), E: epinephrine (pg/ml), P: pulse (beats per min), SBP and DBP: systolic and diastolic blood pressure (mm Hg); 1, 2, and 3 indicate times 1-3 (i.e., 20 min supine, 30 supine, and 15 min standing, respectively). Significant differences are identified in the text.

statistical significance is reported for all tests as two-tailed $p \leq 0.05$, except where otherwise specified.

Results

Group Comparisons

Twenty-four patients with panic attacks with or without agoraphobia, 8 patients with GAD, and 32 normal subjects were studied. The mean age (\pm standard deviation) for the groups was 33.1 (7.0) years for panic patients, 31.6 (4.6) for GAD, and 31.3 (8.8) for normal subjects. The percentage of women in the three groups was 58%, 62%, and 38%, respectively; by chi-square analysis this difference was not significant.

Group means (\pm standard deviations) for all pretreatment variables are presented in Table 1; numbers of subjects studied for each variable in each group are also presented. By ANOVA, the maximum number of clonidine binding sites (B_{max}) was significantly different across the three groups ($F = 6.33$, $df = 2,57$, $p < 0.005$); by regression analysis the amount of variance accounted for by diagnosis (R^2) was 14%. Post hoc Scheffe' tests indicated that the mean B_{max} 's for both the panic and the GAD groups were significantly lower than the mean B_{max} for the normal subjects.

The overall F -tests were also significant for the apparent dissociation constant for clonidine (K_D) ($F = 4.70$, $df = 2,57$, $p < 0.02$; $R^2 = 3\%$) and for the yohimbine B_{max}

($F = 3.98$, $df = 2,58$, $p < 0.03$; $R^2 = 12\%$). Post hoc Scheffe' tests indicated that, for the clonidine K_D , the GAD group was significantly lower than the normal subjects, and for the yohimbine B_{max} , the panic group was significantly lower than the normal subjects. None of the ANOVAs for any of the other group means reached statistical significance. However, there was a trend toward significance for standing systolic blood pressure ($F = 3.21$, $df = 2,35$, $p < 0.06$) and for the change from supine to standing systolic blood pressure ($F = 2.72$, $df = 2,35$, $p < 0.08$). These trends were due to the lower systolic blood pressure in the GAD patients; 3 of these patients had decreases in systolic pressure upon standing, associated with complaints of dizziness (Table 1). The differences in gender ratios between the patient groups and the normal subject group did not influence these results.

For 20 of the panic patients, history of medication use was available for the 2-month period prior to study. Ten of the patients had been free of prescription medications during this time and the other 10 had received a variety of psychotropic and other medications. Means and standard deviations for the four binding parameters for drug-free and for nondrug-free panic patients were as follows: clonidine B_{max} (femtomol/mg protein)—drug free = 29.5 (12.8), nondrug-free = 22.3 (10.1); yohimbine B_{max} (femtomol/mg protein)—drug-free = 91.9 (29.1), nondrug-free = 121 (35.3); clonidine K_D (nM)—drug-free = 5.51 (3.49), nondrug-free = 4.70 (1.86); yohimbine K_D (nM)—drug-free = 3.23 (1.41), nondrug-free = 3.35 (1.13). None of these differences were significant; the difference for the yohimbine B_{max} showed a trend ($t = 2.04$, $df = 18$, $p < 0.06$), but the difference for the clonidine B_{max} did not approach significance ($t = 1.38$, $df = 17$, $p = 0.19$). The yohimbine B_{max} for the 10 drug-free patients for at least 2 months was significantly lower than the B_{max} for the 31 normal subjects [(Table 1) $t = 3.43$, $p < 0.01$]. None of the other values for either 2-month drug-free or nondrug-free patients differed from the values for the normal subjects (Table 1).

Five of the 17 panic patients who were evaluated were positive for MVP, whereas 1 of 8 GAD patients was positive for MVP; by chi-square analysis, this difference was not significant. Patients with MVP had lower systolic (93 versus 109 mm Hg, $t = 2.63$, $df = 13$, $p < 0.03$) and diastolic (54 versus 67 mm Hg, $t = 2.41$, $df = 13$, $p < 0.04$) blood pressures after 20 min supine. There was no significant difference for either systolic or diastolic pressures at the other two times; however, MVP-positive patients were at least 7 mm Hg lower for both systolic and diastolic pressures after 30 min supine and after 15 min standing. No other physiological variable differed significantly between those patients who did and those who did not have MVP, but the B_{max} for yohimbine demonstrated a trend for MVP-positive patients to have fewer binding sites than MVP-negative patients (82 versus 109 fmol/mg protein, $t = 2.13$, $df = 14$, $p < 0.06$).

Correlational Findings for Physiological Variables

Pearson product-moment correlations were performed for the four binding parameters with each other and with the other physiological variables. Correlations of the binding variables with each other and with the other physiological variables were performed for all subjects, and separately for the three diagnostic groups (panic patients, GAD patients, and normal subjects). Because of the large number of correlations performed, the more conservative probability level of 0.01 for the r -value was chosen as the criterion for significance. Because some of the variables might not be normally distributed, Spearman's ρ (correlation for ranked data) was calculated for each r -value that was significant.

Table 2. Correlations of Binding Parameters with Other Physiological Variables

	All Subs		Panic Pats		GAD Pats	All Pats	Normal Sub
	Cl B _{max}	Y K _D	Cl B _{max}	Y K _D	Y K _D	Cl B _{max}	Cl B _{max}
Cl K _D <i>r</i>	+0.44 ^b		+0.58 ^b			+0.56 ^b	
<i>rho</i>	+0.41 ^b		+0.45 ^a			+0.38 ^a	
NE ₂₀ <i>r</i>					-0.93 ^b		
<i>rho</i>					-0.89 ^a		
NE _{mean} <i>r</i>					-0.92 ^b		
<i>rho</i>					-0.82 ^a		
NE _{incr} <i>r</i>	+0.39 ^b						
<i>rho</i>	+0.36 ^a						
E ₂₀ <i>r</i>		+0.58 ^b		+0.79 ^b			
<i>rho</i>		+0.50 ^b		+0.56 ^b			
E ₃₀ <i>r</i>		+0.56 ^b					
<i>rho</i>		+0.46 ^a					
E _{mean} <i>r</i>				+0.74 ^b			
<i>rho</i>				+0.51 ^a			
P _{incr30} <i>r</i>							+0.79 ^b
<i>rho</i>							+0.76 ^a
P _{incr mean} <i>r</i>							+0.83 ^b
<i>rho</i>							+0.75 ^a
SBP ₃₀ <i>r</i>				+0.64 ^b			
<i>rho</i>				+0.54 ^a			

^a*p* < 0.05; ^b*p* < 0.01.

Groups analyzed include all subjects (subs), panic disorder patients (panic pats), generalized anxiety disorder patients, all patients, normal subjects. Cl: tritiated clonidine (a partial alpha₂-adrenergic receptor agonist for the platelet receptor); Y: tritiated yohimbine (a platelet alpha₂-adrenergic receptor antagonist); B_{max}: maximum number of binding sites (femtomol/mg protein); K_D: apparent dissociation constant (nmol); NE: norepinephrine (pg/ml); E: epinephrine (pg/ml); P: pulse (beats per min); SBP: systolic blood pressure (ml of mercury); *r*: Pearson product-moment correlation coefficient; *rho*: Spearman rank-correlation coefficient. Subscripts: 20-20 min supine; 30-30 min supine; mean: average of 20- and 30-min values; incr: increase from level referred to by other subscript to level at 15-min standing.

Correlations are reported as significant only if *p* < 0.01 for the *r*-value and *p* < 0.05 for the more conservative Spearman's *rho*. All correlations reaching these criteria are presented in Table 2.

Based on an analysis of all subjects, the clonidine B_{max} was significantly correlated with the clonidine K_D and with the magnitude of the increase in norepinephrine upon standing. The clonidine B_{max} and K_D were not significantly correlated with any other physiological variables. The yohimbine K_D was significantly correlated with supine plasma epinephrine at both time points; the yohimbine B_{max} was not significantly correlated with any other physiological variable.

Based on inclusion of panic patients only, the clonidine B_{max} was significantly correlated with the clonidine K_D; the same correlations were not significant for patients with GAD (*r* = +0.45) or normal subjects (*r* = +0.12), but was significant based on the inclusion of both patient groups. The yohimbine K_D was significantly correlated with (1) plasma epinephrine after 20 min supine, (2) mean of plasma epinephrine after 20 and after 30 min supine, and (3) systolic blood pressure after 30 min supine. No other correlations were significant for this patient group.

For the patients with GAD, there were significant *negative* correlations for the yohimbine K_D with plasma norepinephrine after 20 min supine and with the mean of the

plasma norepinephrine levels after 20 min and 30 min supine. No other correlations were significant for this group.

For normal subjects, the clonidine B_{max} was significantly correlated with the increase in pulse upon standing, as determined either by the change in pulse from 30 min supine to 15 min standing or by the change in the mean supine pulse (20 min and 30 min) to the pulse after 15 min standing. No other correlations were significant for this group.

The only significant correlation with age was for the change in norepinephrine level when going from supine to standing for normal subjects ($r = +0.84$, $\rho = +0.92$, both $p < 0.01$). The same correlations for patients were panic ($r = +0.10$, $\rho = +0.06$), and GAD ($r = +0.58$, $\rho = +0.58$).

In addition to determining those correlations that were significantly different from zero, correlations were compared across the three diagnostic groups to determine if any were significantly different from each other. Using the criterion of $p < 0.05$, sporadic differences were observed, but none were significantly different from each other by the more stringent criterion of $p < 0.01$. This may be due, at least in part, to small sample sizes for some comparisons (sample sizes for specific comparisons can be determined from Table 1).

Correlational Findings for Symptoms

Panic patients had symptom ratings over 1 week while drug free in addition to determination of binding and other physiological variables, as described above. The clonidine B_{max} and the clonidine K_D were significantly correlated with the severity of full unexpected attacks ($r = +0.55$ and $+0.64$, $p < 0.05$ and 0.02 , respectively). There were no other significant symptom correlations for clonidine binding, and there were no significant correlations for yohimbine binding with any of the symptom variables. Separate correlations for the four binding parameters with number of attacks, duration of attacks, and intensity of attacks for the four different types of attacks demonstrated a pattern of magnitudes of correlations similar to the results for the total severity scores (not shown).

Discussion

The results of this study indicate that the clonidine B_{max} was significantly lower in both of the patient groups than in normal subjects; the yohimbine B_{max} was also significantly lower in panic patients, and somewhat lower in GAD patients as well, as reported previously (Sevy et al. 1989). Additionally, the clonidine K_D was significantly lower in GAD, but not panic, patients. Among the other physiological variables (supine and standing levels of systolic and diastolic blood pressure, pulse, and venous plasma epinephrine and norepinephrine), no significant differences were observed other than a decrease in blood pressure upon standing in some of the GAD patients; further study will be needed to determine if this abnormality of standing blood pressure in some GAD patients is replicable. Thus, the results of this study (1) agree with those prior studies that did not report abnormalities of catecholamines, pulse, and blood pressure in panic patients; and (2) indicate that GAD patients also are normal on these physiological variables under the conditions of this study. The actual values of these physiological variables were consistent with prior reports of levels in normal subjects (Cryer 1980; Ziegler and Lake 1984; Weiner 1985; Cameron et al. 1987a).

The lower yohimbine B_{max} in panic patients is consistent with our prior result (Cameron

et al. 1984); however, our prior study reported a normal level for the clonidine B_{max} , whereas in this study the clonidine B_{max} was also decreased. It is not certain why this discrepancy occurred; however, the sample size for clonidine binding determinations was substantially larger in this study than in the prior study (22 panic patients and 31 normal subjects versus 11 panic patients and 13 normal controls), suggesting that the results of the present study might be more reliable. It is also possible that effects of prior drug exposure between 2 months and 10 days before study influenced the results; there was a nonsignificant tendency for patients who were drug free for at least 2 months to have clonidine B_{max} 's closer to normal than did patients who were not drug free for this length of time. (In contrast, for the yohimbine B_{max} , the results for drug-free versus nondrug-free patients were in the opposite direction.) Further research will be necessary to clarify this issue.

Although the present study replicates our prior finding (Cameron et al. 1984) of decreased yohimbine binding in panic patients and agrees with one other report (Albus et al. 1986), studies by Nutt and Fraser (1987) and Charney et al. (1989a) did not find any decrease. The study by Nutt and Fraser, however, used intact platelets rather than isolated platelet membranes and reported a total number of binding sites that was less than 50% of the number in the present study; approximately 25% of the subjects in the study by Charney et al. (1989a) also reached current criteria for major depression. Thus, these two studies might not be comparable to the present study. The other study of platelet α_2 -adrenergic receptor binding that found no difference (Norman et al. 1987) used a different tritiated ligand, rauwolscine; thus, this study also might not be comparable to the present research. It will be important to determine the actual reason(s) for the discrepancy in study outcomes.

Although the percentage of patients with MVP was not significantly different between panic and GAD, the difference observed suggested that the percentage of panic patients might actually be greater, as has been suggested previously (Dager et al. 1986a). The percentage of MVP-positive panic patients in this study agreed with the percentage reported in prior studies (Nesse et al. 1985a; Dager et al. 1986a, 1986b; Gorman et al. 1986, 1988b; Cameron and Nesse 1988; Margraf et al. 1988). The lower blood pressures in MVP-positive patients in comparison to MVP-negative patients is consistent with prior research which has reported autonomic abnormalities in people with MVP (see Weissman et al. 1987; Cameron and Nesse 1988).

There was a significant positive correlation between the clonidine B_{max} and the clonidine K_D for patients but not for normal subjects. There were significant positive correlations for clonidine B_{max} with norepinephrine increase upon standing and, for normal subjects only, with increase in pulse upon standing. Clonidine B_{max} and K_D were also significantly positively correlated with severity of full unexpected panic attacks in panic patients. Sporadic significant correlations were observed for the yohimbine K_D ; these correlations did not suggest any consistent pattern. The significant association between age and increase in norepinephrine upon rising which was observed in normal subjects was weaker in GAD patients and absent in people with panic attacks. In summary, the number of agonist binding sites, although not necessarily significantly different between patients and normal subjects, appears to be the platelet α_2 -adrenoreceptor binding parameter most closely associated with other physiological and symptom measures.

These results demonstrate that receptor binding abnormalities can occur in association with normal catecholamine levels, suggesting that this receptor abnormality is a primary defect and not down-regulation secondary to elevated circulating catecholamine levels,

as suggested by some prior research (Cameron et al. 1984; Sevy et al. 1989). These results do not exclude the possibility that plasma catecholamine levels are elevated intermittently in anxious patients under conditions not tested in this study, and that these intermittent elevations are producing platelet α_2 -adrenergic receptor down-regulation. Some prior studies have suggested that such increases can occur. However, it is not clear what differences in situations and/or patients led to some reports of normal levels and other reports of elevations; perhaps surprisingly, plasma catecholamine and MHPG levels do not appear to be significantly increased during unexpected (Cameron et al. 1987b), lactate-induced (Liebowitz et al. 1985; Carr et al. 1986), or caffeine-induced (Charney et al. 1985) anxiety and panic attacks. It is possible that patients are more reactive to stressful circumstances than are normal subjects, and that adrenergically mediated physiological variables show excessive increases in anxious patients in those circumstances, but are normal under minimally stressful situations such as those in the present study (Albus et al. 1987, 1988; see also Cameron and Nesse 1988).

As noted above, further research is needed regarding the possibility that receptor changes are due, at least in part, to prior drug exposure in the patient groups, irrespective of any effects on circulating catecholamine levels. It is not known how much time after discontinuation of a drug affecting the platelet α_2 -adrenergic receptor is required for binding to return to predrug levels. The duration might be longer than the standard 10–14 days usually used, and might differ among drugs. Furthermore, different binding parameters might require different durations; for example, the data described above for panic patients suggest that the clonidine B_{max} might be sensitive to prior drug exposure up to 2 months before study whereas the yohimbine B_{max} might not be reactive (or might be in the other direction).

The results of the correlational analyses indicated that the maximum number of binding sites (B_{max}) was significantly positively correlated with the apparent dissociation constant (K_D) only for the α_2 -adrenergic receptor agonist tritiated clonidine. The B_{max} for tritiated clonidine was also significantly positively correlated with postural change in plasma norepinephrine and, for panic patients, with severity of full unexpected panic attacks. Significant correlations for binding of the antagonist tritiated yohimbine with other variables did not appear to demonstrate any consistent pattern. Significant correlations for binding of an agonist, but not for an antagonist, are consistent with the hypothesis that other physiological variables should be correlated with the receptor in its functional state; agonist binding is more reflective of the functional state of receptors than is antagonist binding (U'Pritchard 1984). In addition, the significant correlation of tritiated clonidine binding with unexpected, but not with situational, panic attacks is consistent with the idea that the physiological status of the receptor is influential in determining the severity of unexpected panic attacks whereas environmental variables are stronger determinants of situational attacks.

An issue of importance in the interpretation of the results of this study is the question of the relationship between platelet α_2 -adrenergic receptors and the α_2 -adrenergic receptors on neurons; in other words, of what potential importance for nervous system functioning is the status of a receptor on a platelet? As noted above, there is evidence that, in some ways, the platelet behaves similar to a monoaminergic neuron. Additionally, the locus of the gene coding for the platelet α_2 -adrenergic receptor appears to have been located (Kobilka et al. 1987), documenting that the status of this receptor is at least in part under genetic control. Finally, the occurrence of panic disorder (and possibly other anxiety disorders as well) appears to be at least partially genetically determined (Crowe

et al. 1988). Thus, it is possible that the alpha₂-adrenergic receptor abnormality on the platelet is indicative of a (genetically determined?) abnormality which is present in the nervous system of anxious individuals as well as on the platelet. Despite some inconsistencies in the results of studies of the relationship between alpha₂-adrenergic receptors and other adrenergic variables (Baker and Drew 1981; FitzGerald et al. 1981; Lees 1981; Motulsky et al. 1981; Davies et al. 1981, 1982; Snavely et al. 1983, 1985; Hollister et al. 1983; Siever et al. 1983; Cameron et al. 1984; Mills and Dimsdale 1988), the presence of an abnormality of alpha₂-adrenergic receptors in the nervous systems of individuals with pathological anxiety would be consistent with the hypothesized existence of adrenergic dysregulation in these individuals. Dysregulation of adrenergic functioning rather than abnormalities of absolute levels of adrenergic markers such as blood pressure, pulse, and circulating catecholamines might account for the discrepancies in the results of prior studies of these adrenergic marker variables in anxious people.

The question of the potential relationship between the status of alpha₂-adrenergic receptors in the peripheral nervous system and the status of receptors in the CNS is also important. If the etiological dysfunction in people with anxiety disorders is in the CNS, as seems likely, then the status of the alpha₂-adrenergic receptor in the CNS is of primary interest. As reviewed above, there is evidence from both infusion and neuroimaging studies that CNS alpha₂-adrenergic receptors are functioning abnormally in anxious individuals. There is controversy over the possibility of an association between the status of adrenergic functioning in the periphery and in the CNS; some studies suggest such a relationship but others do not (Maas and Leckman 1983; Hamilton et al. 1985; Hamilton and Reid 1986; Nutt 1987; Svensson 1987). Thus, the abnormality of the platelet alpha₂-adrenergic receptor might or might not reflect dysfunction of this receptor in the CNS as well as in the peripheral nervous system in anxious patients.

As reviewed above, prior pharmacological challenge studies and in vitro beta-adrenergic binding studies do not clearly distinguish panic and generalized anxiety patients from patients with major depressive disorder. In contrast, platelet alpha₂-adrenergic binding studies do appear to differentiate anxiety disorder patients from those with major depressive disorder. Furthermore, platelet binding results suggest that patients with mixed panic-major depression have an adrenergic abnormality similar to panic, but dissimilar from uncomplicated major depression. A complete characterization of adrenergic function in psychiatric disorders will require (1) study of different diagnostic groups, including those with mixed symptomatology, and (2) determination of adrenergic status in these patients with a variety of adrenergic markers and probes.

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References

- Aarons RD, Molinoff PB (1982): Changes in the density of beta adrenergic receptors in rat lymphocytes, heart and lung after chronic treatment with propranolol. *J Pharmacol Exp Ther* 221:439-443.
- Aarons RD, Nies AS, Gerber JG, Molinoff PB (1983): Decreased beta adrenergic receptor density on human lymphocytes after chronic treatment with agonists. *J Pharmacol Exp Ther* 224:1-6.
- Abrams WB, Solomon HM (1969): The human platelet as a pharmacologic model for the adrenergic neuron: The uptake and release of norepinephrine. *Clin Pharmacol Ther* 10:702-709.

- Albus M, Bondy B, Ackenheil M (1986): Adrenergic receptors on blood cells: Relation to the pathophysiology of anxiety. *Clin Neuropharmacol* 9(Suppl 4):359-361.
- Albus M, Braune S, Hohn T, Scheibe G (1988): Do anxiety patients with or without frequent panic attacks differ in their response to stress? *Stress Med* 4:189-194.
- Albus M, Muller-Spahn F, Ackenheil M, Engel RR (1987): Psychiatric patients and their response to experimental stress. *Stress Med* 3:233-238.
- Amsterdam JD, Maislin G, Skolnick B, Berwisch N, Wiokur A (1989): Multiple hormone responses to clonidine administration in depressed patients and normal volunteers. *Biol Psychiatry* 26:265-278.
- Aronson TA, Carasiti I, McBane D, Whitaker-Azmitia P (1989): Biological correlates of lactate sensitivity in panic disorder. *Biol Psychiatry* 26:463-477.
- Baker DJ, Drew GM (1981): An investigation into the possible physiological roles of vascular alpha₁- and alpha₂-adrenoreceptors. *J Auton Pharmacol* 1:359-365.
- Ballenger JC, Peterson GH, Laraia M, et al (1984): A study of plasma catecholamines in agoraphobia and the relationship of serum tricyclic levels to treatment response. In Ballenger JC (ed), *Biology of Agoraphobia*. Washington, DC: American Psychiatric Press, pp 27-63.
- Balon R, Ortiz A, Pohl R, Yeragani VK (1988): Heart rate and blood pressure during placebo-associated panic attacks. *Psychosom Med* 50:434-438.
- Brodde OE, Kretsch R, Ikezono K, Zerkowsky HR, Reidemeister JC (1986): Human beta-adrenoreceptors: Relation of myocardial and lymphocyte beta-adrenoreceptor density. *Science* 231:1584-1585.
- Brown SL, Charney DS, Woods SW, Heninger GR, Tallman J (1988): Lymphocyte beta-adrenergic receptor binding in panic disorder. *Psychopharmacology* 94:24-28.
- Cameron OG, Curtis GC, Zelnik T, et al (1987a): Circadian fluctuation of plasma epinephrine in supine humans. *Psychoneuroendocrinology* 12:41-51.
- Cameron OG, Lee MA, Curtis GC, McCann DS (1987b): Endocrine and physiological changes during "spontaneous" panic attacks. *Psychoneuroendocrinology* 12:321-331.
- Cameron OG, Nesse RM (1988): Systemic hormonal and physiological abnormalities in anxiety disorders. *Psychoneuroendocrinology* 13:287-307.
- Cameron OG, Smith CB, Hollingsworth PJ, Nesse RM, Curtis GC (1984): Platelet alpha₂-adrenergic receptor binding and plasma catecholamines: Before and during imipramine treatment in patients with panic anxiety. *Arch Gen Psychiatry* 41:1144-1148.
- Campbell IC (1981): Blood platelets and psychiatry. *Br J Psychiatry* 138:78-80.
- Carr DB, Sheehan DV, Surman OF, et al. (1986): Neuroendocrine correlates of lactate-induced anxiety and their response to chronic alprazolam therapy. *Am J Psychiatry* 143:483-494.
- Carstens ME, Engelbrecht AH, Russell VA, Aalbers C, Gagiano CA, Chalton DO, Taljaard JF (1987): Beta-adrenoreceptors on lymphocytes of patients with major depressive disorder. *Psychiatry Res* 20:239-248.
- Castellani S, Quillen MA, Vaughan DA, et al. (1988): TSH and catecholamine response to the TRH in panic disorder. *Biol Psychiatry* 24:87-90.
- Charney DS, Heninger GR (1986): Abnormal regulation of noradrenergic function in panic disorders: Effects of clonidine in healthy subjects and patients with agoraphobia and panic disorder. *Arch Gen Psychiatry* 43:1042-1054.
- Charney DS, Heninger GR, Breier A (1984): Noradrenergic function in panic anxiety: Effects of yohimbine in healthy subjects and patients with agoraphobia and panic disorder. *Arch Gen Psychiatry* 41:751-763.
- Charney DS, Heninger GR, Jatlow PI (1985): Increased anxiogenic effects of caffeine in panic disorders. *Arch Gen Psychiatry* 42:233-243.
- Charney DS, Heninger GR, Sternberg DE, Hafstad KM, Griddings S, Landis DH (1982): Adrenergic receptor sensitivity in depressive illness. *Arch Gen Psychiatry* 39:290-294.

- Charney DS, Innis RB, Duman RS, Woods SW, Heninger GR (1989a): Platelet alpha-2-receptor binding and adenylate cyclase activity in panic disorder. *Psychopharmacology* 98:102-107.
- Charney DS, Woods SW, Goodman WK, Heninger GR (1987): Neurobiological mechanisms of panic anxiety: Biochemical and behavioral correlates of yohimbine-induced panic attacks. *Am J Psychiatry* 144:1030-1036.
- Charney DS, Woods SW, Heninger GR (1989b): Noradrenergic function in generalized anxiety disorder: Effects of yohimbine in healthy subjects and patients with generalized anxiety disorder. *Psychiatry Res* 27:173-182.
- Checkley SA, Slade AP, Shur H (1981): Growth hormone and other responses to clonidine in patients with endogenous depression. *Br J Psychiatry* 138:51-55.
- Cohen RM, Campbell IC, Dauphin M, Tallman JF, Murphy DL (1982): Changes in alpha- and beta-receptor densities in rat brain as a result of treatment with monoamine oxidase inhibiting antidepressants. *Neuropharmacology* 21:293-298.
- Cole JC (1984): Beta-adrenergic blockers and buspirone. In Grinspoon L (ed), *Psychiatric Update, Vol. III*. Washington, DC: American Psychiatric Press, pp 490-503.
- Crow A, Glover V, Weg MW, et al. (1988): Urinary catecholamine metabolite and tribulin output during lactate infusion. *Br J Psychiatry* 152:122-126.
- Crowe RR, Noyes R, Persico T, Wilson HF, Elston RC (1988): Genetic studies of panic disorder and related conditions. In Dunner DL, Gershon ES, Barrett JE (eds), *Relatives at Risk for Mental Disorder*. New York: Raven Press, pp 73-85.
- Cryer PE (1980): Physiology and pathophysiology of the human sympathoadrenal neuroendocrine system. *N Engl J Med* 303:436-444.
- Curtis GC, Glitz DA (1988): Neuroendocrine findings in anxiety disorders. *Neurol Clin N Am* 6:131-148.
- Curtis G, Lee MA, Glitz DA, Cameron OG, Abelson J, Bronzo M (1989): Growth hormone response to clonidine in anxiety disorders (Abstract). *Biol Psychiatry* 25:6A.
- Dager SR, Comess KA, Dunner DL (1986a): Differentiation of anxious patients by two-dimensional echocardiographic evaluation of the mitral valve. *Am J Psychiatry* 143:533-535.
- Dager SR, Comess KA, Saal AK, Dunner DL (1986b): Mitral valve prolapse in a psychiatric setting: Diagnostic assessment, research and clinical implication. *Integr Psychiatry* 4:211-223.
- Davies B, Sudera D, Sagnalla G, et al. (1982): Increased numbers of alpha receptors in sympathetic denervation supersensitivity in man. *J Clin Invest* 69:779-784.
- Davies IB, Sudera D, Sever PS (1981): Endogenous agonist regulation of alpha-adrenoceptors in man. *Clin Sci* 61:207s-210s.
- Dubacovitch ML (1984): Presynaptic alpha-adrenoceptors in the central nervous system. In Salama AI (ed), *Presynaptic Modulation of Postsynaptic Receptors in Mental Disease* (Vol. 430). New York: New York Academy of Sciences, pp 7-25.
- Edlund MJ, Swann AC, Davis CM (1987): Plasma MHPG in untreated panic disorder. *Biol Psychiatry* 22:1488-1491.
- Egan B, Neubig K, Julius S (1985): Pharmacologic reduction of sympathetic drive increases platelet alpha-2-receptor number. *Clin Pharmacol Ther* 38:519-524.
- Extein I, Tallman J, Smith CC, Goodwin FK (1979): Changes in lymphocyte beta-adrenergic receptors in depression and mania. *Psychiatry Res* 1:191-197.
- FitzGerald GA, Watkins J, Dollery CT (1981): Regulation of norepinephrine release by peripheral alpha₂-receptor stimulation. *Clin Pharmacol Ther* 29:160-167.
- Fraser J, Nadeau J, Robertson D, Wood AJJ (1981): Regulation of human leukocyte beta receptors by endogenous catecholamines: Relationship of leukocyte beta receptor density to the cardiac sensitivity to isoproterenol. *J Clin Invest* 67:1777-1784.
- Freedman RR, Ianni P, Etedgui E, Pohl R, Rainey JM (1984): Psychophysiological factors in panic disorder. *Psychopathology* 17(Suppl 1):66-73.

- Galant SP, Duriseti L, Underwood S, Insel PA (1978): Decreased beta-adrenergic receptors on polymorphonuclear leucocytes after adrenergic therapy. *N Engl J Med* 299:933-936.
- Garcia-Sevilla JA, Hollingsworth PJ, Smith CB (1981a): Alpha₂-adrenoreceptors on human platelets: Selective labelling by [³H]clonidine and [³H]yohimbine and competitive inhibition by antidepressant drugs. *Eur J Pharmacol* 74:329-341.
- Garcia-Sevilla JA, Zis AP, Hollingsworth PJ, Greden JF, Smith CB (1981b): Platelet alpha₂-adrenergic receptors in major depressive disorder. *Arch Gen Psychiatry* 41:1327-1333.
- Gorman JM (1984): The biology of anxiety. In Grinspoon L (ed), *Psychiatry Update, Vol. III*. Washington, DC: American Psychiatric Press, Inc, pp 467-482.
- Gorman JM, Battista D, Goetz RR, et al. (1989): A comparison of sodium bicarbonate and sodium lactate infusion in the induction of panic attacks. *Arch Gen Psychiatry* 46:145-150.
- Gorman JM, Fyer MR, Goetz R, et al. (1988a): Ventilatory physiology of patients with panic disorder. *Arch Gen Psychiatry* 45:31-39.
- Gorman JM, Goetz RR, Fyer M, et al. (1988b): The mitral valve prolapse-panic disorder connection. *Psychosom Med* 50:114-122.
- Gorman JM, Shear MK, Devereux RB, King DL, Klein DF (1986): Prevalence of mitral valve prolapse in panic disorder: Effect of echocardiographic criteria. *Psychosom Med* 48:167-171.
- Grunhaus LJ (1988): Clinical and psychobiological characteristics of simultaneous panic disorder and major depression. *Am J Psychiatry* 145:1214-1221.
- Grunhaus LJ, Cameron OG, Pande AC, Haskett RF, Hollingsworth PJ, Smith CB (1989): Comorbidity of panic disorder and major depressive disorder: Effects on platelet alpha₂-adrenergic receptors. *Acta Psychiatr Scand* (in press).
- Hamilton CA, Jones CR, Mishra N, Barr S, Reid JL (1985): A comparison of alpha₂-adrenoreceptor regulation in brain and platelets. *Brain Res* 347:350-353.
- Hamilton CA, Reid JL (1986): Platelet alpha-adrenoreceptors—A valid model for brain or vascular adrenoreceptors? *Br J Clin Pharmacol* 22:623-626.
- Heninger GR, Charney DS, Price LH (1988): Alpha₂-adrenergic receptor sensitivity in depression: The plasma MHPG, behavioral, and cardiovascular responses to yohimbine. *Arch Gen Psychiatry* 45:718-726.
- Hoehn-Saric R, McLeod DR (1988): The peripheral sympathetic nervous system: Its role in normal and pathologic anxiety. *Psychiatr Clin North Am* 11:375-386.
- Hollister AS, FitzGerald GA, Nadeau JHJ, Robertson D (1983): Acute reduction in human platelet alpha₂-adrenoreceptor affinity for agonist by endogenous and exogenous catecholamines. *J Clin Invest* 72:1498-1505.
- Janowsky A, Sulzer D (1987): Alpha and beta adrenoreceptors in brain. In Meltzer HY (ed), *Psychopharmacology: The Third Generation of Progress*. New York: Raven Press, pp 249-256.
- Kziona CLE, Theodorou AE, Horton RW (1987): Alpha₂-adrenoreceptors in depression. *Psychiatr Dev* 2:129-149.
- Ko GN, Elsworth JP, Roth RH, Rifkin BG, Leigh H, Redmond DE (1983): Panic-induced elevation of plasma MHPG levels in phobic-anxious patients. *Arch Gen Psychiatry* 40:425-430.
- Kobilka BK, Matsui H, Kobilka TS, et al. (1987): Cloning, sequencing, and expression of the gene coding of the human platelet alpha₂-adrenergic receptor. *Science* 238:650-656.
- Kosten TR, Mason JW, Giller EL, Ostroff RB, Harkness L (1987): Sustained urinary norepinephrine and epinephrine elevation in post-traumatic stress disorder. *Psychoneuroendocrinology* 12:13-20.
- Krause M, Reinhardt D, Kruse K (1988): Pheochromocytoma without symptoms: Desensitization of the alpha- and beta-adrenoreceptors. *Eur J Pediatr* 147:121-122.
- Langer SZ (1980): Presynaptic regulation of the release of catecholamines. *Pharmacol Rev* 32:337-362.
- Lees GM (1981): A hitch-hiker's guide to the galaxy of adrenoceptors. *Br Med J* 283:173-178.

- Liebowitz MR, Gorman JM, Fyer AJ, et al. (1985): Lactate provocation of panic attacks. II. Biochemical and physiological findings. *Arch Gen Psychiatry* 42:709-719.
- Lima DR, Turner P (1983): Propranolol increases reduced beta-receptor function in severely anxious patients. *Lancet* ii:1505.
- Maas JM, Leckman JF (1983): Relationship between central nervous system noradrenergic function and plasma and urinary MHPG and other norepinephrine metabolites. In Maas JW (ed), *MHPG: Basic Mechanisms and Psychopathology*. New York: Academic Press, pp 33-43.
- Magliozzi JR, Gietzen D, Maddock RJ, et al. (1989): Lymphocyte beta-adrenoreceptor density in patients with unipolar depression and normal controls. *Biol Psychiatry* 26:15-25.
- Mann JJ, Brown RP, Halper JP, et al. (1985): Reduced sensitivity of lymphocyte beta-adrenergic receptors in patients with endogenous depression and psychomotor agitation. *N Engl J Med* 313:715-720.
- Margraf J, Ehlers A, Roth WT (1988): Mitral valve prolapse and panic disorder: A review of their relationship. *Psychosom Med* 50:93-113.
- Margraf J, Taylor CB, Ehlers A, Roth WT, Agras WS (1987): Panic attacks in the natural environment. *J Nerv Ment Dis* 175:558-565.
- Mathew RJ, Ho BT, Kralik P, Taylor DL, Claghorn JL (1981): Catecholamine and monoamine oxidase activity in anxiety. *Acta Psychiatr Scand* 63:245-252.
- Mathew RJ, Wilson WH (1986): Hematocrit and anxiety. *J Psychosom Res* 30:307-311.
- Matussek N, Ackenheil M, Hippus H, et al. (1980): Effect of clonidine on growth hormone release in psychiatric patients and controls. *Psychiatry Res* 2:25-36.
- Mills PJ, Dimsdale JE (1988): The promise of receptor studies in psychophysiological research. *Psychosom Med* 50:555-566.
- Motulsky HJ, O'Connor DT, Insel PA (1983): Platelet alpha₂-adrenergic receptors in treated and untreated essential hypertension. *Clin Sci* 64:265-272.
- Munson PJ, Rodbard D (1980): LIGAND: A versatile computerized approach for characterization of ligand binding systems. *Anal Biochem* 107:220-239.
- Nesse RM, Cameron OG, Buda AJ, McCann DS, Curtis GC, Huber-Smith MH (1985a): Urinary catecholamines and mitral valve prolapse in panic anxiety patients. *Psychiatry Res* 14:67-74.
- Nesse RM, Cameron OG, Curtis GC, McCann DS, Huber-Smith MH (1984): Adrenergic function in patients with panic anxiety. *Arch Gen Psychiatry* 41:771-776.
- Nesse RM, Curtis GC, Thyer BA, McCann DS, Huber-Smith MH, Knopf RF (1985b): Endocrine and cardiovascular responses during phobic anxiety. *Psychosom Med* 47:320-332.
- Norman TR, Kimber NM, Judd FK, Burrows GD, McIntyre IM (1987): Platelet ³H-rauwolscine binding in patients with panic attacks. *Psychiatry Res* 22:43-48.
- Noyes R (1985): Beta-adrenergic blocking drugs in anxiety and stress. *Psychiatr Clin North Am* 8:119-132.
- Nutt DJ (1987): Platelet alpha₂-adrenoreceptor binding does not predict brain alpha₂-adrenoreceptor function. *Br J Clin Pharmacol* 24:122-123.
- Nutt DJ (1989): Altered central alpha₂-adrenoreceptor sensitivity in panic disorder. *Arch Gen Psychiatry* 46:165-169.
- Nutt DJ, Cowan PJ (1987): Monoamine function in anxiety and depression: Information from neuroendocrine challenge tests. *Hum Psychopharmacol* 2:211-220.
- Nutt DJ, Fraser S (1987): Platelet binding studies in panic disorder. *J Affect Disord* 12:7-11.
- Pandey GN, Dysken MW, Garver DL, Davis JM (1979): Beta-adrenergic receptor function in affective illness. *Am J Psychiatry* 136:675-678.
- Pecquery R, Leneveu M-C, Giudicelli Y (1984): In vivo desensitization of the beta, but not the alpha₂-adrenoreceptor-coupled-adenylate cyclase system in hamster white adipocytes after administration of epinephrine. *Endocrinology* 114:1576-1583.

- Perry BD, Biller EL, Southwick SM (1987): Altered platelet alpha₂-adrenergic binding sites in posttraumatic stress disorder. *Am J Psychiatry* 144:1511-1512.
- Pfeifer MA, Ward K, Malpass T, et al. (1984): Variations in circulating catecholamines fail to alter human platelet alpha-2-adrenergic receptor number or affinity for [³H]yohimbine or [³H]dihydroergocryptine. *J Clin Invest* 74:1063-1072.
- Pohl R, Etedgui E, Bridges M, et al. (1987): Plasma MHPG levels in lactate and isoproterenol anxiety states. *Biol Psychiatry* 22:1127-1136.
- Racagni G, Mocchetti I, Calderini G, Battistella A, Brunello N (1983): Temporal sequence of changes in central noradrenergic system of rat after prolonged antidepressant treatment: Receptor desensitization and neurotransmitter interactions. *Neuropharmacology* 22:415-424.
- Redmond DE (1979): New and old evidence for the involvement of a brain norepinephrine system in anxiety. In Fann WF, Karacan I, Porkorny AD, Williams (eds), *Phenomenology and Treatment of Anxiety*. New York: SP Medical and Scientific Books, pp 153-203.
- Roy-Byrne PP, Uhde TW (1985): Panic disorder and major depression: Biological relationships. *Psychopharmacol Bull* 21(3):551-554.
- Schittecatte M, Charles G, Depauw Y, Mesters P, Wilmotte J (1988): Growth hormone response to clonidine in panic disorder patients. *Psychiatry Res* 23:147-151.
- Schneider N, Evans L, Ross-Lee L, et al. (1987): Plasma biogenic amine levels in agoraphobia with panic attacks. *Pharmacopsychiatry* 20:102-104.
- Sevy S, Papadimitriou GN, Surmont DW, Goldman S, Mendlewicz J (1989): Noradrenergic function in generalized anxiety disorder, major depressive disorder, and healthy subjects. *Biol Psychiatry* 25:141-152.
- Shear MK, Kingfield P, Harshfield G, et al. (1987): Cardiac rate and rhythm in panic patients. *Am J Psychiatry* 144:633-637.
- Sheehan DV (1986): *The Anxiety Disease* (Revised Paperback ed). New York: Bantam Books.
- Sheehan DV, Coleman JH, Greenblatt DJ, et al. (1983): Some biochemical correlates of panic attacks with agoraphobia and their response to a new treatment. *J Clin Psychopharmacol* 4:66-75.
- Siever LJ, Pickar D, Lake CR, Cohen RM, Uhde TW, Murphy DL (1983): Extreme elevations in plasma norepinephrine associated with decreased alpha-adrenergic responsivity in major depressive disorder: Two case reports. *J Clin Psychopharmacol* 3:39-41.
- Siever LJ, Uhde TW (1984): New studies and perspectives on the noradrenergic receptor system in depression: Effects of the alpha₂-adrenergic agonist clonidine. *Biol Psychiatry* 19:131-156.
- Smith CB, Garcia-Sevilla JA, Hollingsworth PJ (1981): Alpha₂-adrenoreceptors in rat brain are decreased after long-term tricyclic antidepressant drug treatment. *Brain Res* 210:413-418.
- Snavely MD, Mahan LC, O'Connor DT, Insel PA (1983): Selective down-regulation of adrenergic receptor subtypes in tissues from rats with pheochromocytoma. *Endocrinology* 113:354-361.
- Snavely MD, Ziegler MG, Insel PA (1985): Subtype-selective down-regulation of rat renal cortical alpha- and beta-adrenergic receptors by catecholamines. *Endocrinology* 117:2182-2189.
- Spitzer RL, Endicott J (1985): *Schedule for Affective Disorders and Schizophrenia—Lifetime Version (Modified for the Study of Anxiety Disorders)*. New York: New York State Psychiatric Institute Biometrics Research Department.
- Spitzer RL, Endicott J, Robins E (1978): Research diagnostic criteria: Rationale and reliability. *Arch Gen Psychiatry* 35:773-782.
- Spitzer RL, Williams JBW (1983): *Instruction Manual for the Structured Clinical Interview for DSM-III (SCID)*. New York: New York State Psychiatric Institute Biometrics Research Department.
- Spitzer RL, Williams JBW (1988): Revised diagnostic criteria and a new structured interview for diagnosing anxiety disorders. *J Psychiatr Res* 22(Suppl 1):55-85.
- Stahl SM (1977): The human platelet: A diagnostic and research tool for the study of biogenic amines in psychiatric and neurologic disorders. *Arch Gen Psychiatry* 34:509-516.

- Starke K (1981): Presynaptic receptors. *Annu Rev Pharmacol Toxicol* 21:7-30.
- Stein MB, Uhde TW (1988): Cortisol response to clonidine in panic disorder: Comparison with depressed patients and normal controls. *Biol Psychiatry* 34:322-330.
- Svensson TH (1987): Peripheral, autonomic regulation of locus coeruleus noradrenergic neurons in brain: Putative implications for psychiatry and psychopharmacology. *Psychopharmacology* 92:1-7.
- Task Force on Nomenclature and Statistics (1980): *Diagnostic and Statistical Manual of Mental Disorders [ed 3 (DSM-III)]*. Washington, DC: American Psychiatric Association.
- Taylor CB, Sheikh J, Agras WS, et al. (1986): Ambulatory heart rate changes in patients with panic attacks. *Am J Psychiatry* 143:478-482.
- Tsujimoto G, Manger WM, Hoffman BB (1984): Desensitization of beta-adrenergic receptors by pheochromocytoma. *Endocrinology* 114:1272-1278.
- Uhde TW, Joffe RT, Jimerson DC, Post RM (1988): Normal urinary-free cortisol and plasma MHPG in panic disorder: Clinical and theoretical implications. *Biol Psychiatry* 23:575-585.
- Uhde TW, Stein MB, Vittone BJ, et al. (1989): Behavioral and physiological effects of short-term and long-term administration of clonidine in panic disorder. *Arch Gen Psychiatry* 46:170-177.
- Uhde TW, Vittone BJ, Siever LJ, Kaye WH, Post RM (1986): Blunted growth hormone response to clonidine in panic disorder patients. *Biol Psychiatry* 21:1077-1081.
- U'Pritchard DC (1984): Biochemical characteristics and regulation of brain alpha₂-adrenoreceptors. In Salama AI (ed), *Presynaptic Modulation of Postsynaptic Receptors in Mental Diseases* (Vol. 430). New York: Academy of Sciences, pp 55-75.
- Ursano RJ (1985): Catecholamines in anxiety disorders and mitral valve prolapse. In Lake CR, Ziegler MG (eds), *The Catecholamines in Psychiatric and Neurologic Disorders*. Boston: Butterworth Publishers, pp 75-89.
- Villacres EC, Hollifield M, Katon WJ, Wilkinson CW, Veith RC (1987): Sympathetic nervous system activity in panic disorder. *Psychiatry Res* 21:313-321.
- Weiner N (1985): Norepinephrine, epinephrine, and the sympathomimetic amines. In Gilman AG, Goodman LS, Rall TW, Murad F (eds), *The Pharmacological Basis of Therapeutics* (ed 7). New York: MacMillan Publishing Co, pp 145-180.
- Weissman NJ, Shear MK, Kramer-Fox R, Devereux RB (1987): Contrasting patterns of autonomic dysfunction in patients with mitral valve prolapse and panic attacks. *Am J Med* 82:880-888.
- White WB, Baker LH (1986): Episodic hypertension secondary to panic disorder. *Arch Intern Med* 146:1129-1130.
- Wood K, Whiting K, Coppen A (1986): Lymphocyte beta-adrenergic receptor density of patients with recurrent affective illness. *J Affect Disord* 10:3-8.
- Woods SW, Charney DS, Goodman WK, Heninger GR (1988a): Carbon dioxide-induced anxiety: Behavioral, physiologic, and biochemical effects of carbon dioxide in patients with panic disorders and healthy subjects. *Arch Gen Psychiatry* 45:43-52.
- Woods SW, Charney DS, McPherson CA, Gradman AH, Heninger GR (1987): Situational panic attacks. *Arch Gen Psychiatry* 44:365-375.
- Woods SW, Koster K, Krystal JK, et al. (1988b): Yohimbine alters regional cerebral blood flow in panic disorder. *Lancet* ii:678.
- Ziegler MG, Lake CR (1984): *Norepinephrine*. Baltimore: Williams and Wilkins.