Association of β-Endorphin With Specific Clinical Symptoms of Depression

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Objective: *Abnormalities in plasma concentrations of β-endorphin-like immunoreactivity (β-endorphin) have been reported in depressed patients. This study was done to test the hypothesis that specific clinical characteristics of depression are associated with plasma β-endorphin concentration.* *Method:* *Plasma β-endorphin was evaluated in 20 depressed patients diagnosed according to* DSM-III-R *and in 23 age- and sex-matched comparison subjects, and each was evaluated with the structured Schedule for Affective Disorders and Schizophrenia (SADS). Twelve SADS items involving dysphoric mood and related symptoms were chosen for analysis.* *Results:* *Within the group of all 43 subjects and within the depressed group, β-endorphin level correlated significantly with psychic anxiety and with phobia. In the depressed group only, β-endorphin also correlated significantly with obsessions/compulsions. Concentration of β-endorphin was not significantly correlated with score on the Hamilton Rating Scale for Depression or Beck Depression Inventory or with scores on other SADS symptom items, including somatic anxiety, insomnia, subjective anger, overt anger, agitation, psychomotor retardation, panic attacks, appetite loss, or total weight loss. In the group of 23 comparison subjects, β-endorphin did not correlate with Beck or Hamilton depression score or with any of the SADS clinical variables.* *Conclusions:* *High levels of plasma β-endorphin may be associated with more severe anxiety, phobia, and obsessions/compulsions in depressed patients.*

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Beta-endorphin is a 31-amino-acid hormone released by the pituitary into the systemic circulation in response to various psychological and physiological stimuli (1, 2). High basal plasma levels of β-endorphin and greater than normal secretion of β-endorphin in response to cholinergic stimulation have been observed in previous studies of depressed patients (3, 4), although not in all (5). Adults with affective psychiatric illness and early parental loss have been found to have higher resting plasma levels of β-endorphin than do healthy comparison subjects with early parental loss (6), and a lower than normal total β-lipotropin/β-endorphin secretory response after infusion of corticotropin-releasing factor has been found in depressed patients (5). Other studies (7–9) have shown nonsuppression of plasma β-endorphin after dexamethasone administration in depressed patients in whom dexamethasone also did not suppress cortisol, even in patients whose baseline β-endorphin levels were not higher than normal. Postdexamethasone levels of cortisol and β-endorphin were strongly positively correlated (8, 9).

In the present study we tested the hypothesis that high degrees of specific clinical characteristics (symptoms) of depression are associated with higher than normal plasma levels of β-endorphin-like immunoreactivity (referred to here as "β-endorphin"). Using the items involving dysphoric mood and related symptoms from the structured Schedule for Affective Disorders and Schizophrenia (SADS) interview, we examined the following 12 clinical characteristics of depression: somatic anxiety, psychic anxiety, phobia, insomnia, subjective feelings of anger, overt expression of anger, agitation, psychomotor retardation, panic attacks, obsessions/compulsions, appetite loss, and total weight

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loss. Concentration of β-endorphin, severity of depressed mood, and these 12 symptoms were measured in 20 depressed patients and 23 age- and sex-matched comparison subjects.

METHOD

Subjects

The subject group comprised 43 subjects, 20 patients and 23 age- and sex-matched (all male) normal comparison subjects. The patients ranged in age from 29 to 71 years, and the comparison subjects' ages ranged from 31 to 68 years; their mean ages were 43 (SD=11) and 44 (SD=10), respectively ($t=-0.30$, $df=41$, $p=0.8$). They were hospitalized of clinical necessity but on a voluntary basis. All of the patients in the study gave informed consent.

Each patient completed a SADS interview (10) conducted by a research fellow in psychiatry. Twelve individual items from the SADS section on dysphoric mood and related symptoms were chosen. Eight of these items have an interval rating of severity and are parametric variables; the remaining four are nonparametric categorical variables. These items were used in the analyses. (SADS dysphoria items that describe core dysphoria/depression symptoms were not used. Subjective feelings of depression, negative evaluation of self, and similar SADS items were not included because they are so uniformly present in all depressed patients that we felt they would poorly discriminate depression subtypes.)

Research diagnoses were made in a consensus meeting of three psychiatrists and were based on the *DSM-III-R* nosologic system. The diagnoses of the 20 patients were as follows: major depression, recurrent (N=13), major depression, single episode (N=3), and bipolar disorder not otherwise specified (bipolar II) (N=4). All of the patients were currently depressed. Severity of depression was measured with the clinically objective 21-item Hamilton Rating Scale for Depression (11) and the subjective 21-item Beck Depression Inventory (12).

The patients' diagnoses of substance dependence were as follows: no history of alcohol or other substance abuse or dependence (N=10), diagnosis of alcohol dependence (N=4), alcohol dependence, in remission (N=2), alcohol abuse (N=2), alcohol abuse, in remission (N=1), and amphetamine dependence, in remission (N=1). The physical health of each patient was assessed through medical history, physical examination, CBC with WBC differential count, CHEM 20 blood chemistry profile, measurement of serum cholesterol and triglyceride levels, thyroid studies (T_3, T_4), rapid plasma reagin test for syphilis, urinalysis, and ECG. Patients with medical histories or conditions that may have affected this study were excluded. Some of the subjects involved in this study also volunteered for other studies, which have been described elsewhere (13–18). Although all of the patients had previously been treated with medication, all were hospitalized and had been free of medication and of alcohol and other substances of abuse for at least 14 days before this study. None of the patients had been treated with fluoxetine, which has a long half-life, before the study.

The 23 comparison subjects were medically and psychiatrically healthy and were recruited from a large metropolitan area. The comparison subjects were not admitted to the hospital, were not currently mentally ill, and had no history of mental illness according to SADS interview. The physical health of each comparison subject was assessed through medical history and CBC with WBC differential count.

β-*Endorphin Assay*

With standard clinical technique, venous blood was drawn into EDTA anticoagulated tubes. Three different protocols for blood drawing were used over the total time of the study. For 45% of the patients (N=9) and 40% of the comparison subjects (N=9), a single venipuncture in an antecubital fossa vein provided the single sample used. For 35% of the patients (N=7) and 30% of the comparison subjects (N=7), a butterfly needle was placed in a forearm vein, and three samples were drawn at 30, 45, and 60 minutes after needle placement. For 20% of the patients (N=4) and 30% of the comparison subjects (N=7), a blood sample was drawn immediately after butterfly needle placement, followed by samples at 30, 45, and 60 minutes. When multiple samples were drawn, the average β-endorphin level was used in the analysis. No time effect was observed for subjects from whom multiple samples were drawn. The plasma was collected by centrifugation of the blood samples at 400 *g* for 15 minutes, and it was kept frozen at –80 °C until thawed for the β-endorphin radioimmunoassay.

The β-endorphin was measured by using the Nichols solid-phase iodine-125 two-site immunoradiometric assay. All samples were assayed in duplicate and within the same assay. The intra-assay coefficient of variation was 4.4%. The sensitivity of the assay is 10 pg/ml with a 16% cross-reactivity to human β-lipotropin. Two of the depressed patients had β-endorphin levels that were much higher than the others. These samples were assessed again, and similar values were obtained.

Statistical Analysis

The 20 patients and 23 comparison subjects were included in the analyses. For all analyses, a value of $p<0.05$ was considered significant. Differences in degrees of freedom reflect occasional missing data. (Most of the missing data were for the comparison subjects; the majority of these subjects were completely asymptomatic.) Because of the two patients with high β-endorphin levels, the β-endorphin data (in picograms per milliliter) did not fit a normal distribution. After consultation with a statistician, we log normalized the data, and the $\log_{10}$ of each β-endorphin value was used in the

TABLE 1. Levels of β-Endorphin and Continuous Symptom Variables of 20 Depressed Patients and 23 Comparison Subjects

Variable	Depressed Patients		Comparison Subjects		t Test for Independent Samples		
	Mean	SD	Mean	SD	t	df[a]	p
Hamilton depression score[b]	24	10	1	1	10.09	19.60	<0.0009
Beck depression score[c]	21	10	1	1	8.64	18.73	<0.0009
Plasma β-endorphin level (pg/ml)	36.2	48.0	25.4	15.7	0.54	41	0.6
Scores on SADS items							
Somatic anxiety	2.6	1.3	1.1	0.3	4.86	20.32	<0.0009
Psychic anxiety	3.3	1.3	1.4	0.7	3.98	25	0.001
Insomnia	4.2	1.3	1.3	0.5	8.62	24.87	<0.0009
Subjective anger	3.3	1.4	1.5	1.0	4.00	30	<0.0009
Agitation	2.5	1.4	1.0	0.1	4.60	17.00	<0.0009
Psychomotor retardation	3.0	1.3	1.1	0.3	6.18	20.16	<0.0009
Phobia	2.0	1.4	1.2	0.6	2.16	26.34	0.04
Overt anger	2.0	1.2	1.3	0.7	1.68	26	0.1

[a]Integer df's are for pooled-variance t tests; noninteger df's are for separate-variance t tests; the separate-variance t test was used when the variances of the two groups were significantly different.
[b]On the 21-item Hamilton Rating Scale for Depression.
[c]On the 21-item Beck Depression Inventory.

TABLE 2. Between-Groups Analyses of Scores on Categorical Symptom Variables of 20 Depressed Patients and 23 Comparison Subjects

SADS Item	Mean Rank[a]		Mann-Whitney U	Wilcoxon Rank Sum W	Correction for Ties	
	Depressed Patients	Comparison Subjects			z	p
Panic attacks	19.68	11.85	63	154	−2.6483	0.008
Obsessions/compulsions	18.89	13.00	78	169	−2.4151	0.01
Appetite	20.26	11.00	52	143	−3.2486	0.001
Weight loss	18.94	11.92	64	155	−2.4218	0.01

[a]Rank in nonparametric statistical test.

TABLE 3. Correlations of β-Endorphin Level With SADS Symptom Scores for Combined Depressed and Comparison Subjects and for Depressed Patients

Group and SADS Item	Correlation of β-Endorphin Level With SADS Item Score		
	r	df	p
All subjects (N=43)			
Psychic anxiety	0.42	25	0.03
Phobia	0.44	30	0.01
Somatic anxiety	0.32	30	0.07
Panic attacks	0.30	30	0.09
Obsessions/compulsions	0.30[a]	30	0.09
Depressed patients (N=20)			
Psychic anxiety	0.58	16	0.01
Phobia	0.58	17	0.009
Obsessions/compulsions	0.49[a]	17	0.03
Somatic anxiety	0.40	17	0.09

[a]Spearman's rank-order correlation coefficient for nonparametric (categorical) variables.

statistical analyses. All statistics were calculated by using standard statistical programs (19, 20).

We used t tests for independent samples to test for the significance of the between-groups differences in the continuous variables, and the Mann-Whitney U/Wilcoxon rank sum W test or the Kruskal-Wallis one-way analysis of variance (ANOVA) and chi-square analysis were used for between-groups differences in the categorical variables (panic attacks, obsessions/compulsions, appetite loss, and total weight loss).

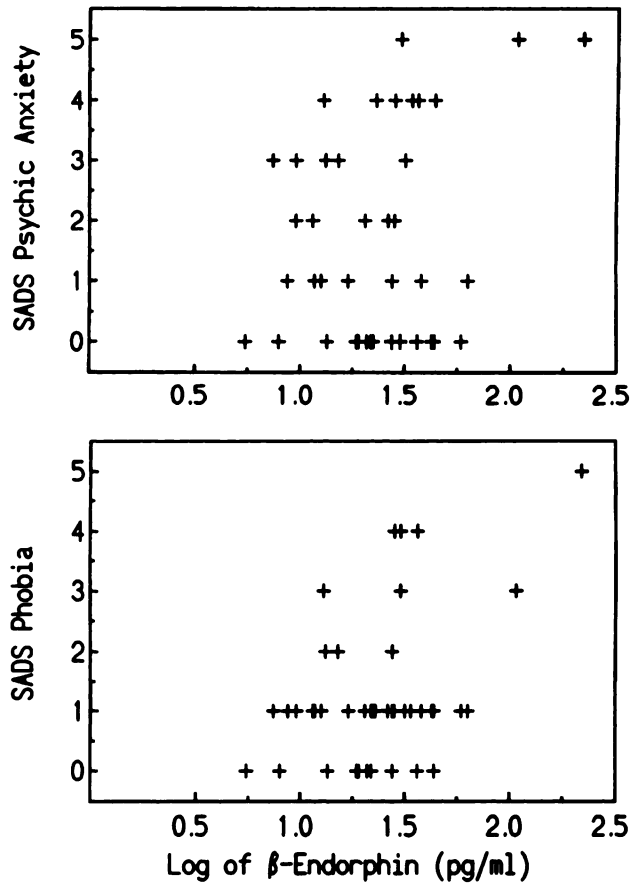
Parametric correlations of the continuous variables were calculated by using Pearson's correlation coefficient (r), and nonparametric correlations of the categorical variables were calculated with Spearman's rank-order correlation coefficient (r_s).

RESULTS

Characteristics of the two groups are shown in table 1. The Hamilton and Beck depression scores of the two groups were markedly and significantly different. Although the patients had a higher mean plasma β-endorphin level than the comparison subjects, the difference did not reach significance.

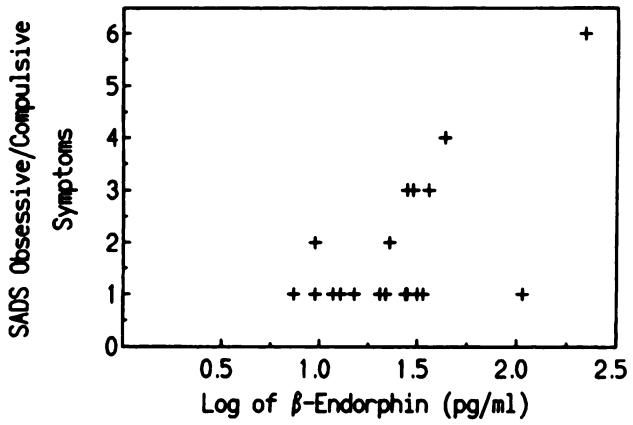
There were significant differences in the scores of the two groups on 11 of the 12 SADS mood items that clinically characterize depression; the patients had significantly more severe somatic anxiety, psychic anxiety, insomnia, subjective feelings of anger, agitation, psychomotor retardation, phobia, panic attacks, and obsessions/compulsions than the comparison subjects (see tables 1 and 2), but the patients did not have significantly more overt expressions of anger. Table 2 presents the results of the Mann-Whitney U/Wilcoxon rank sum W test for panic attacks, obsessions/compulsions, appetite, and weight loss. In addition to significantly more panic attacks and obsessions/compulsions, the patients showed significantly poorer appetite and greater total weight loss.

FIGURE 1. Relation of β-Endorphin Level to SADS Psychic Anxiety and Phobia Scores for Combined Depressed and Comparison Subjects (N=43)[a]



[a]Significant correlations for both psychic anxiety (r=0.42, df=41, p=0.03) and phobia (r=0.44, df=41, p=0.01).

FIGURE 2. Relation of β-Endorphin Level to SADS Obsessions/Compulsions Score for 20 Depressed Patients



Within the group of all 43 subjects, β-endorphin concentration correlated significantly with psychic anxiety and with phobia (table 3 and figure 1). There was no significant correlation in this group between β-endorphin and score on the Hamilton or Beck depression scale or any of the other SADS items assessed, although a nearly significant difference was found for somatic anxiety, for panic attacks, and for obsessions/compulsions (table 3).

Within the group of the 20 patients, β-endorphin correlated significantly with psychic anxiety, with phobia, and with obsessions/compulsions (table 3 and figure 2). There was not a significant correlation between β-endorphin and Hamilton or Beck depression score or score on any of the other SADS items, although a nearly significant correlation was found for somatic anxiety (table 3). Within the group of all 23 comparison subjects, there were no significant correlations between β-endorphin and any of the SADS variables.

The 10 patients with histories of recent or past substance abuse were examined separately to see whether substance abuse history affected the interaction between β-endorphin and the relevant SADS variables. Age, Hamilton score, Beck score, β-endorphin level, and scores for somatic anxiety, psychic anxiety, phobia, and obsessions/compulsions were not significantly different between the patient groups with and without histories of substance abuse (see table 4). For the nonparametric variable, obsessions/compulsions, the results of Kruskal-Wallis one-way ANOVA and chi-square analysis were as follows: patients *with* substance abuse history, mean rank=10.17; patients *without* substance abuse history, mean rank=9.85 (χ^2=0.02, df=1, p=0.8, n.s.). For the 10 patients with substance abuse histories, β-endorphin did not significantly correlate with any of the other variables (0.1<p<0.7).

DISCUSSION

This study, designed to test the hypothesis that plasma β-endorphin concentration in depressed patients is associated with specific clinical characteristics of depression, demonstrated a significant association between β-endorphin and three specific symptoms of depression as elicited by SADS interview—psychic anxiety, phobia, and obsessions/compulsions—and further suggested a possible association between β-endorphin and somatic anxiety and panic attacks.

Except for overt expressions of anger, the groups were significantly different in the symptoms chosen for study. There were no significant correlations between β-endorphin and the SADS interview items in the comparison group. This finding may support the specificity of the association between β-endorphin and anxiety, phobia, and obsessions/compulsions in the patients. An equally likely explanation, however, is that the narrow range of responses by the comparison subjects to the SADS items (most were scored zero) made it difficult to find significance on statistical tests for correlations.

The β-endorphin level was higher in the patient group but not significantly so. The literature is currently in conflict as to the true association between depression

TABLE 4. Age, β-Endorphin Level, and Selected Symptom Scores of 20 Depressed Patients With and Without Histories of Substance Abuse

	With Abuse History (N=10)		Without Abuse History (N=10)		ANOVA		
Variable	Mean	SD	Mean	SD	F	df	p
Age (years)	40	9	47	13	2.88	1, 17	0.1
Hamilton depression score[a]	23	8	26	13	0.002	1, 17	0.9
Beck depression score[b]	19	11	22	10	0.54	1, 17	0.5
Plasma β-endorphin level (pg/ml)	30.7	29.1	41.7	62.9	0.68	1, 17	0.4
Scores on SADS items							
Somatic anxiety	2.8	1.2	2.4	1.3	0.97	1, 16	0.3
Psychic anxiety	3.5	1.4	3.1	1.2	0.42	1, 16	0.5
Phobia	2.0	1.3	2.0	1.5	0.03	1, 16	0.9

[a]On the 21-item Hamilton Rating Scale for Depression.
[b]On the 21-item Beck Depression Inventory.

and β-endorphin (3, 4, and 6 versus 5, 7–9). This conflict may have resulted from inattention to specific symptoms characterizing depression.

The results support the concept that β-endorphin is associated with specific clinical symptom clusters in depression, specifically symptoms associated with anxiety states. The results support the recent conceptualization of broad overlap between the depression spectrum of illnesses and the anxiety disorders. Anxiety and depression may have a common neurological substrate (21). In multivariate genetic analysis (22), no evidence could be found for genes that specifically affect symptoms of depression without also strongly influencing symptoms of anxiety. In a recent study of twin pairs (23), the results suggested an etiologic relationship between mixed major depression/anxiety disorders and major depression. Patterns of relationships of anxiety and depression to sociodemographic factors, prior psychopathology, and life events do not distinguish the two syndromes (24), and most widely used assessment methods do not measure anxiety and depression independently (25). Almost 40% of patients with *DSM-III* anxiety disorders simultaneously fulfill the criteria for a depressive disorder, mainly major depression (26). Lactate-infusion-induced decreases in β-endorphin have not distinguished subjects with major depression from subjects with panic disorder (27). Symptom overlap between depression and anxiety is large. The probability of symptom overlap in 150 psychiatric outpatients has been found to be 56%–60% (28). Finally, in a study of physically active versus sedentary men (29), the physically active men had a lower mean plasma β-endorphin level, lower anxiety index, and lower depression score than did the sedentary men. The literature regarding the relation of anxiety to depression has been reviewed by Stavrakaki and Varge (30).

Future studies may explore hypotheses concerning the specific role of β-endorphin in anxiety and phobia within the context of depression. Further, there is a growing interest in defining specific mental illnesses in terms of biological substrates rather than clusters of clinical symptoms or "phenotypic expression." The mapping of biological markers with clinical symptoms is a necessary step in this nosologic progress.

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