Lymphocyte Glucocorticoid Receptor Number in Posttraumatic Stress Disorder

Rachel Yehuda, Ph.D., Martin T. Lowy, Ph.D., Steven M. Southwick, M.D., Dottie Shaffer, B.S., and Earl L. Giller, Jr., M.D., Ph.D.

Objective: The authors' objective was to investigate the possibility that glucocorticoid receptor changes may be involved in the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis in posttraumatic stress disorder (PTSD). Method: They measured the number of lymphocyte cytosolic glucocorticoid receptors and plasma cortisol concentrations in 15 consecutively admitted male combat Vietnam veterans with PTSD and in a normal comparison group of 11 subjects. Results: Both the patients and the normal comparison subjects showed a morning-to-afternoon decline in glucocorticoid receptor concentrations, paralleling the normal diurnal decline in cortisol levels. The number of glucocorticoid receptors was 63% greater in the morning and 26% greater in the afternoon in the patients with PTSD than in the normal subjects. No group differences in cortisol levels were observed, nor were glucocorticoid receptor number and cortisol levels correlated. The number of morning glucocorticoid receptors was positively correlated with symptoms of PTSD and anxiety. Conclusions: These results provide further evidence for a dysregulation of the HPA axis in PTSD. The finding that patients with PTSD had a substantially greater number of lymphocyte glucocorticoid receptors than normal comparison subjects is consistent with the authors' previous observations of low 24-hour urinary cortisol excretion in subjects with PTSD. Furthermore, the receptor changes observed are opposite of those reported in major depressive disorder. The present data, along with other findings of HPA abnormalities in PTSD, support the possibility of a greater negative feedback sensitivity at one or more levels of the HPA axis.
(Am J Psychiatry 1991; 148:499–504)

Although stress is a major etiologic factor in posttraumatic stress disorder (PTSD), there have been surprisingly few investigations of the hypothalamic-pituitary-adrenal (HPA) axis in this disorder. Despite the paucity of studies, however, there is emerging evidence for HPA dysfunction in chronic PTSD. Moreover, the biological data seem to distinguish PTSD from other psychiatric disorders such as major depressive disorder.

Previous work in our laboratory has shown that patients with PTSD have lower urinary-free cortisol levels than patients with major depressive disorder (1) and normal comparison subjects (2). Consistent with these data, the cortisol response to the standard 1-mg dose of dexamethasone has been found to be either within the normal range (3, 4) or exaggerated (5) in PTSD. In contrast, major depression has been associated with hypercortisolemia, which in a subgroup of patients is reflected in nonsuppression of cortisol in response to dexamethasone (6).

There is also evidence for a blunted ACTH response to corticotropin-releasing factor (CRF) in patients with PTSD (7). A blunted ACTH response to CRF has also been observed in major depressive disorder; however, the mechanisms underlying this response are likely to be different in the two disorders. In PTSD, the attenuated ACTH response occurred in the presence of normal afternoon plasma cortisol levels (7). In contrast, in major depressive disorder a blunted ACTH response occurs with hypercortisolemia, possibly reflecting a lower number of pituitary CRF receptors caused by hypothalamic CRF hypersecretion (8, 9) and/or an altered negative feedback inhibition of the pituitary (10).

In the aggregate, the findings of low cortisol excretion and blunted ACTH responses to CRF in chronic

Received Dec. 6, 1989; revision received Aug. 16, 1990; accepted Sept. 25, 1990. From the Psychiatry Service, West Haven VA Medical Center, Conn., and the Psychiatry Department, Case Western Reserve University Medical School, Cleveland. Address reprint requests to Dr. Yehuda, Psychiatry Department, University of Connecticut Health Center, Farmington, CT 06032.

Supported by NIMH postdoctoral training grant MH-17122 (Dr. Yehuda), NIMH grants MH-44339 and MH-44699 (Dr. Lowy), and VA Merit Award research funds (Dr. Southwick).

The authors thank John Krystal, M.D., for helpful comments and John Roach for technical assistance.

TABLE 1. Age and Clinical Information for 15 Patients With PTSD

Subject	Age (years)	Medications	Comorbid RDC Diagnosis	Hamilton Anxiety Score	Hamilton Depression Score	Mississippi PTSD Score
1	41	Buspirone	Substance abuse	27	22	147
2	37	Diazepam, imipramine, perphenazine	Major depressive disorder	38	35	191
3	42	Desipramine	None	11	9	123
4	37	Tranylcypromine	Substance abuse	21	23	144
5	39	Clonidine	Substance abuse	16	15	132
6	39	Imipramine	Panic disorder	28	28	136
7	39	Lorazepam, diphenhydramine	Major depressive disorder	20	33	129
8	39	Temazepam, desipramine, propranolol	None	34	24	137
9	39	Clonidine	None	24	24	112
10	39	None	Substance abuse	20	22	115
11	39	None	Major depressive disorder	15	16	107
12	42	None	Substance abuse	14	19	117
13	40	None	None	17	22	122
14	37	None	Major depressive disorder	17	32	112
15	45	None	Major depressive disorder	19	24	137

PTSD suggest a disturbance in adrenocortical regulation, which may be due to alterations in tissue sensitivity and/or negative feedback at one or more levels of the HPA axis, perhaps secondary to changes in hormone receptor sensitivity. Because circulating corticosteroid concentrations have been found to produce dynamic changes in the number of glucocorticoid receptors in a variety of target tissues in the brain (11, 12) and lymphocytes (13), the lower cortisol levels observed in chronic PTSD may be associated with an increased number of glucocorticoid receptors in neurons and/or lymphocytes.

An altered negative feedback sensitivity within the HPA axis has also been postulated in major depressive disorder. In this case, feedback sensitivity is reported to be less, paralleling the lower number of glucocorticoid receptors in lymphocytes (14, 15). To further investigate the possibility that glucocorticoid receptor changes may be involved in the dysregulation of the HPA axis in PTSD, we measured morning and afternoon plasma cortisol concentrations and the number of glucocorticoid receptors in circulating lymphocytes in patients with chronic PTSD and in a normal comparison group.

METHOD

Fifteen consecutively admitted male Vietnam combat veterans (age range=37–45 years, mean±SD=39.5±2.1, median=40) with a primary diagnosis of PTSD and 11 healthy men (age range=30–56 years, mean=37.8±7.48, median=37) participated in the study after giving voluntary, written informed consent. PTSD was diagnosed by using the Structured Clinical Interview for DSM-III-R (SCID) (16) and the Mississippi Scale for Combat-Related PTSD (17); a cutoff of 107 was used on the Mississippi scale. Other diagnoses were made according to *DSM-III-R* by consensus from results of structured diagnostic interviews (SCID or the Schedule for Affective Disorders and Schizophrenia) and assessments by the treating psychiatrist and ward chief. Five of the 15 patients had a comorbid diagnosis of major depressive disorder, and five had comorbid substance abuse or dependence. Patients were excluded if they met criteria for a psychotic or organic condition; had substantial medical illness as determined by history, physical examination, and routine laboratory screening; regularly used more than 3 oz of absolute alcohol per day; or had used street drugs within 3 weeks of the drawing of blood. Nine of the 15 patients were being treated with medications, including antidepressants and anxiolytics.

Blood was obtained by venipuncture at 8:00 a.m. and 4:00 p.m., and mononuclear cells were isolated by using Ficoll Hypaque within 1 hour following the drawing of blood. Cells were centrifuged at 300 *g* at 4 °C, washed four times in ice-cold Hank's buffer, and pelleted. An aliquot of the lymphocyte suspension was counted by a Coulter counter, and the final pellet was stored at −70 °C. An aliquot of plasma was also frozen for subsequent determination of cortisol levels.

Clinical ratings were made by two raters (R.Y. and S.M.S.) on the day blood was drawn. Anxiety and depression were assessed by using the Hamilton Rating Scale for Anxiety (18) and the Hamilton Rating Scale for Depression (19). Patients also completed the Mississippi Scale for Combat-Related PTSD (17), which served as both a diagnostic instrument and a measure of severity of combat PTSD.

Combat exposure was rated on a scale of 0–56 by using the expanded Combat Exposure Scale (20). Pa-

TABLE 2. Effect of Comorbidity on Cortisol and Number of Glucocorticoid Receptors in 15 Patients With PTSD[a]

	Number of Glucocorticoid Receptors				Plasma Cortisol Level (μg/dl)			
	Morning		Afternoon		Morning		Afternoon	
Group	Mean	SD	Mean	SD	Mean	SD	Mean	SD
PTSD with major depressive disorder (N=5)	3702	1317	1657	873	16.1	3.1	6.6	1.5
PTSD without major depressive disorder (N=10)	3366	1379	1726	970	12.8	2.8	8.9	3.5
PTSD with substance abuse (N=5)	3004	1050	1760	1356	13.2	3.9	7.6	3.2
PTSD without substance abuse (N=10)	3694	1617	1675	680	15.0	3.4	8.5	3.3

[a]The small number of subjects in this analysis raises the possibility of a type II error.

tients were also interviewed with the Atrocity Scale (21), which quantifies exposure to and/or participation in particularly traumatic combat-related behaviors on a scale of 6–36 (6=no experience of any atrocities and 36=active participation in all).

Binding of glucocorticoid receptors was measured with the highly selective type II glucocorticoid ligand ^{3}H-RU 28362 according to Lowy (22). Briefly, the frozen lymphocyte pellets (containing 50–100×10^6 cells) were suspended in the assay buffer (consisting of 10 mM Tris, 1 mM EDTA, 2.5 mM dithiothreitol, 10% glycerol, 20 mM Na_2MoO_4; pH 7.4), mixed vigorously in the cold for 30 minutes, then spun at 250,000 g for 30 minutes. Total binding of ^{3}H-RU 28362 (specific activity=77 Ci/mmol) was measured in 0.25 ml aliquots of cytosol, which were incubated overnight at 4 °C with 10 nM of ligand. Specific binding was defined as that inhibited by a 500-fold excess of unlabeled RU 28362. The 10-nM concentration of ^{3}H-RU 28362 measures 90% of available receptors and correlates highly (r=0.99) with B_{max} values (22).

For the determination of cortisol levels, untreated plasma samples were thawed and cortisol levels analyzed by using a radioimmunoassay kit procedure developed by Clinical Assays, Inc. (Cambridge, Mass.). The interassay coefficient of variation for this method was 4.0%. Binding assays and radioimmunoassays were done blind to the subjects' diagnoses.

Differences between patients with PTSD and normal subjects were assessed with repeated measures (22) two-tailed analysis of variance (ANOVA). Repeated measures ANOVA was also performed to determine the effects of comorbidity of major depressive disorder and substance abuse or dependence and the effects of medication status on biological measures. Clinical data from subgroups of the patients with PTSD were assessed with Student's t test. Post hoc testing was performed with the Tukey test. Correlational analyses were performed with Pearson's r. Group values are expressed as mean±SD.

RESULTS

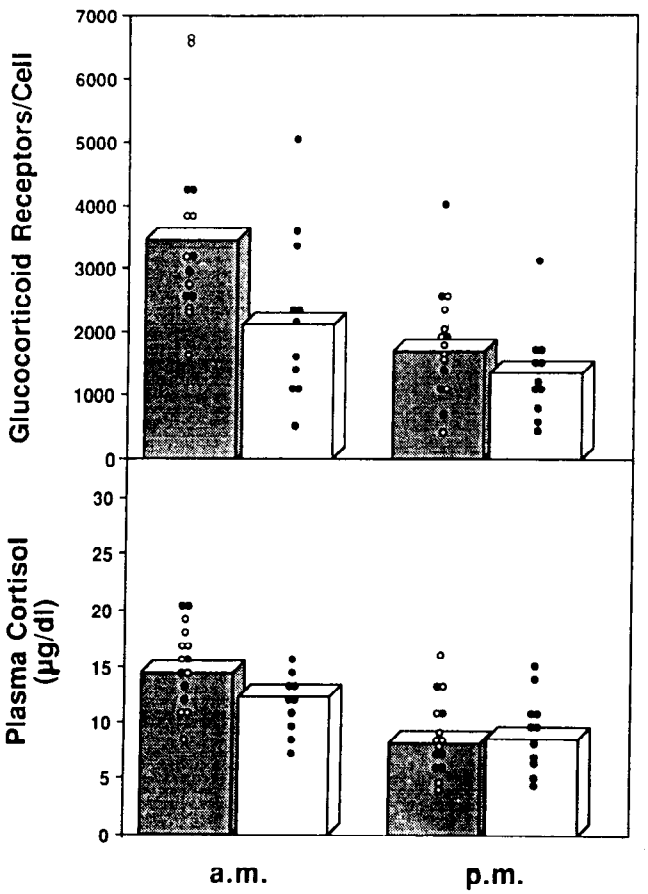
The patients' ages and individual clinical ratings are presented in table 1. Subdividing patients on the basis of presence or absence of major depressive disorder revealed that PTSD patients with comorbid major depressive disorder (N=5) had significantly higher scores than did those without major depressive disorder (N=10) on the Hamilton depression scale (28.0±7.9 versus 20.8±5.3; t=2.10, df=13, p=0.05) but not on the other clinical rating scales. No differences in clinical symptoms were observed between PTSD patients with (N=5) and without (N=10) comorbid substance abuse or dependence. Medicated patients with PTSD (N=9) had significantly higher scores on the Mississippi Scale for Combat-Related PTSD than unmedicated patients (N=6) (139.0±22.2 versus 118.3±10.4; t=2.11, df=13, p=0.05). Medicated patients also tended to have higher Hamilton anxiety scale scores (24.3±8.5 versus 17.0±2.3; t=2.04, df=13, p=0.06).

As a group, the 15 patients with PTSD had a significantly greater number of glucocorticoid receptors than the 11 normal comparison subjects (F=4.79, df=1, 24, p<0.05). This difference was greater in the morning (63% higher; p<0.05) than in the afternoon (26% higher, n.s.). There were no group differences in morning or afternoon plasma cortisol concentrations. There were overall diurnal changes in the number of glucocorticoid receptors and cortisol concentrations: both measures were significantly higher in the morning than in the afternoon (F=30.09, df=1, 24, p<0.0001; figure 1). There was also a trend for a Group by Time interaction in the number of glucocorticoid receptors (F=3.94, df=1, 24, p=0.06), indicating a steeper morning-to-afternoon decline in the number of glucocorticoid receptors in the patients with PTSD. There were no significant differences in biological variables when the patients with PTSD were subdivided on the basis of medication status (figure 1).

No biological differences as a result of comorbidity were found in patients with PTSD (table 2). Therefore, data from all patients were combined for the purpose of correlational analysis.

The morning and afternoon numbers of glucocorticoid receptors were positively correlated in the patients with PTSD (r=0.498, df=13, p<0.05) and in all subjects combined (r=0.517, df=24, p<0.05). Comparison subjects showed a nonsignificant trend toward a relationship between morning cortisol levels and the

FIGURE 1. Cortisol Level and Number of Lymphocyte Glucocorticoid Receptors in 15 Patients With PTSD and 11 Comparison Subjects[a]



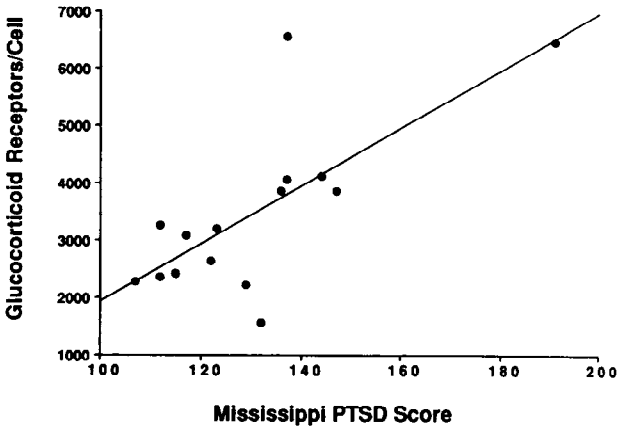
[a]The shaded blocks are patients with PTSD; the unshaded blocks are comparison subjects. Open circles represent medicated patients; closed circles represent unmedicated patients. The morning levels of glucocorticoid receptors in the patients with PTSD were significantly different from those of the comparison subjects ($p<0.05$, post hoc Tukey test).

morning number of glucocorticoid receptors ($r=0.436$, $df=10$, $p=0.18$). This trend was absent in the patients with PTSD ($r=0.189$, $df=14$, $p=0.50$).

The morning number of glucocorticoid receptors was significantly correlated with severity of combat-related PTSD symptoms as assessed by the Mississippi scale (figure 2). It was also significantly correlated with anxiety symptoms measured by the Hamilton anxiety scale ($r=0.784$, $df=14$, $p<0.001$). There was a nonsignificant association between the morning number of glucocorticoid receptors and Hamilton depression scale scores ($r=0.402$, $df=14$, $p<0.10$).

Exposure to combat was not related to the morning number of glucocorticoid receptors ($r=0.032$, $df=12$, n.s.) but was significantly correlated with morning plasma cortisol concentrations ($r=0.489$, $df=12$, $p<0.05$). Scores on the Atrocity Scale were significantly correlated with the morning number of glucocorticoid receptors ($r=0.554$, $df=12$, $p<0.05$) but not with

FIGURE 2. Relationship Between Number of Glucocorticoid Receptors and PTSD Symptoms Assessed by the Mississippi PTSD Scale[a]



[a]$r=0.73$, $df=14$, $p<0.005$.

morning cortisol concentrations ($r=0.018$, $df=12$, n.s.). The Combat Exposure Scale and Atrocity Scale scores were not intercorrelated ($r=0.126$, $df=12$, n.s.) and thus appeared to measure separate dimensions of exposure to stress.

DISCUSSION

The present study demonstrates that patients with PTSD have a substantially greater number of lymphocyte glucocorticoid receptors than normal comparison subjects. These findings are consistent with our previous observations of low 24-hour urinary cortisol excretion in PTSD (1, 2) and provide further evidence for a dysregulation of the HPA axis in PTSD. Furthermore, the receptor changes we observed are opposite of those reported in major depressive disorder (14, 15). In major depressive disorder, changes in HPA function are thought to involve CRF hypersecretion (8, 9), which could occur in response to a decrease in the number of glucocorticoid receptors or sensitivity (10). In contrast, the present data, along with other findings of HPA abnormalities in PTSD, support the possibility of greater negative feedback sensitivity at one or more levels of the HPA axis.

The strong relationship between the number of glucocorticoid receptors and PTSD symptoms as assessed by the Mississippi scale suggests that glucocorticoid receptors may be functionally relevant to PTSD. The significant correlation between the number of glucocorticoid receptors and anxiety symptoms is consistent with the classification of PTSD as an anxiety disorder according to *DSM-III-R*. In contrast, the modest (nonsignificant) correlation between the number of glucocorticoid receptors and Hamilton depression scale scores suggests that changes in the number of glucocorticoid receptors are not likely due to adjunctive symptoms of depression. Related to this, the number

of glucocorticoid receptors was not different in PTSD patients with and without comorbid depression.

There were no differences in the number of glucocorticoid receptors or in cortisol concentrations between medicated and drug-free PTSD patients in our study group. This result agrees with the finding of a previous study that there were no differences in the number of glucocorticoid receptors between medicated and nonmedicated depressed subjects (15). It is possible that our inability to detect specific medication effects was due to the heterogeneous nature of the medication status in the patient group. Further study is required to determine the extent to which medications may affect the number of lymphocyte glucocorticoid receptors.

Lymphocyte glucocorticoid receptors and plasma cortisol levels were measured simultaneously to determine diurnal rhythmicity. When the relationship between plasma cortisol levels and the number of glucocorticoid receptors was examined, no significant correlations were observed in the patient group, the comparison group, or both groups combined. The lack of any relationship between the number of glucocorticoid receptors and plasma cortisol levels could be due to the use of a single cortisol measurement, which may not be an accurate reflection of overall HPA activity due to the episodic nature of cortisol secretion. Other studies measuring the number of glucocorticoid receptors and plasma cortisol levels have also failed to find significant relationships between these measures when using a single cortisol measurement (14, 15, 23, 24). Analysis of the diurnal variation, however, revealed that changes in glucocorticoid receptor levels paralleled diurnal changes in cortisol levels (i.e., the number of glucocorticoid receptors was greater in the morning than in the afternoon). The lack of an inverse relationship between the number of receptors and agonists indicates that the steady-state number of cytosolic glucocorticoid receptors could be influenced by fluctuations in plasma cortisol levels occurring hours before the actual sampling time. The equivalent cortisol levels between the two groups at the time of blood sampling suggest, however, that the greater number of glucocorticoid receptors in the patients with PTSD cannot simply be attributed to cortisol occupation and/or translocation of the cytosolic receptor.

Homologous regulation of glucocorticoid receptors by glucocorticoids has been demonstrated in a variety of tissues (12, 25). However, it is evident that the regulation of glucocorticoid receptors by glucocorticoids is region-specific and not necessarily uniform in all tissues (11, 26). The regulation of lymphocyte glucocorticoid receptors by glucocorticoids in humans has been examined in several studies. Exogenous administration of glucocorticoids can lower the number of lymphocyte glucocorticoid receptors in normal subjects and in patients with leukemia (27). However, regulation of lymphocyte glucocorticoid receptors by endogenous glucocorticoids has not been firmly established. Thus, patients with endocrine disorders resulting in markedly high levels of cortisol (i.e., Cushing's disease) or very low circulating levels of cortisol (i.e., Addison's disease) have relatively normal levels of lymphocyte glucocorticoid receptors (28, 29). In contrast, in psychiatric disorders such as major depressive disorder and anorexia nervosa, which are generally characterized by greater cortisol secretion within the endocrinologically "normal" range, studies have tended to find lower numbers of lymphocyte glucocorticoid receptors. However, as already noted, no significant correlation between the number of glucocorticoid receptors and plasma cortisol levels were observed in those studies (14, 15, 24). Clearly, further studies are required to establish the extent to which lymphocyte glucocorticoid receptors are regulated by endogenous cortisol levels under normal and pathological conditions. In particular, use of 24-hour urine samples may be the measure of choice in elucidating such a relationship. On the other hand, heterologous regulation of lymphocyte glucocorticoid receptors by a variety of nonglucocorticoid factors (30, 31) makes a simple relationship between cortisol levels and the number of glucocorticoid receptors unlikely.

The relationship between the large number of lymphocyte glucocorticoid receptors and neuronal glucocorticoid receptors in PTSD is not known. However, some similarities between lymphoid and neuronal glucocorticoid receptors have been reported in animal studies. For example, high concentrations of glucocorticoid receptors are found in both types of tissues, which are similar in receptor affinity and steroid specificity (32). Lymphoid and neuronal glucocorticoid receptors also share some common regulatory mechanisms; for example, adrenalectomy in rats produces greater numbers of both lymphocyte and hippocampal glucocorticoid receptors (22, 31). If the large number of lymphocyte glucocorticoid receptors in PTSD similarly reflects a large number of hippocampal glucocorticoid receptors, then the HPA abnormalities observed in PTSD could, in fact, be related to greater feedback sensitivity to glucocorticoids. Hippocampal glucocorticoid receptors in particular play a prominent role in stress-induced feedback inhibition of the HPA axis (32) and, therefore, may be an important aspect of HPA dysregulation in PTSD.

REFERENCES

1. Mason JW, Giller EL, Kosten TR, et al: Urinary free cortisol levels in post-traumatic stress disorder patients. J Nerv Ment Dis 1986; 174:145–149
2. Yehuda R, Southwick SM, Nussbaum G, et al: Low urinary cortisol excretion in patients with post-traumatic stress disorder. J Nerv Ment Dis 1990; 178:366–369
3. Kudler H, Davidson J, Meador K, et al: The DST and posttraumatic stress disorder. Am J Psychiatry 1987; 144:1068–1071
4. Kosten TR, Wahby V, Giller E, et al: The dexamethasone test and TRH stimulation test in post traumatic stress disorder, in New Research Program and Abstracts, 141st Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1988
5. Halbreich U, Olympia J, Carson S, et al: Hypothalamo-pitu-

itary-adrenal activity in endogenously depressed post-traumatic stress disorder patients. Psychoneuroendocrinology 1989; 14: 365–370
6. Kathol RG, Jaeckle RS, Lopez JF, et al: Pathophysiology of HPA axis abnormalities in patients with major depression: an update. Am J Psychiatry 1989; 146:311–317
7. Smith MA, Davidson J, Ritchie JC, et al: The corticotropin releasing hormone test in patients with post traumatic stress disorder. Biol Psychiatry 1989; 26:349–355
8. Gold PW, Chrousos GP: Clinical studies with corticotropin releasing factor: implications for the diagnosis and pathophysiology of depression, Cushing's disease and adrenal insufficiency. Psychoneuroendocrinology 1985; 10:401–420
9. Gold PW, Loriaux DL, Roy A: Responses to corticotropin-releasing hormone in the hypercortisolism of depression and Cushing's disease. N Engl J Med 1986; 314:1329–1335
10. Low MT, Gormley GJ, Reder AT, et al: Immune function, glucocorticoid receptor regulation and depression, in Depressive Disorders and Immunity. Edited by Miller AH. Washington, DC, American Psychiatric Press, 1989
11. Sapolsky RM, Krey LC, McEwen BS: Stress down-regulates corticosterone receptors in a site-specific manner in the brain. Endocrinology 1984; 114:287–292
12. McEwen BS, deKloet ER, Rostene WH: Adrenal steroid receptors and actions in the nervous system. Physiol Rev 1986; 66: 1121–1188
13. Schlechte JA, Sherman BM: Decreased glucocorticoid receptor binding in adrenal insufficiency. J Clin Endocrinol Metab 1982; 54:145–149
14. Gormley GJ, Lowy MT, Reder AT, et al: Glucocorticoid receptors in depression: relationship to the dexamethasone suppression test. Am J Psychiatry 1985; 142:1278–1284
15. Whalley LJ, Borthwick N, Copolov D, et al: Glucocorticoid receptors and depression. Br Med J 1986; 292:859–861
16. Spitzer RL, Williams JBW: Structured Clinical Interview for DSM-III-R (SCID). New York, New York State Psychiatric Institute, Biometrics Research, 1985
17. Keane TM, Caddell JM, Taylor KL: Mississippi Scale for Combat-Related Posttraumatic Stress Disorder: three studies in reliability and validity. J Consult Clin Psychol 1988; 56:85–90
18. Hamilton M: The assessment of anxiety states by rating. Br J Med Psychol 1959; 32:50–55
19. Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62
20. Long-Term Stress Reactions: Some Causes, Consequences and Naturally Occurring Support Systems: Legacies of Vietnam: Comparative Adjustment of Veterans and Their Peers, vol 14. Washington, DC, US Government Printing Office, 1981
21. Brett EA: The Atrocity Scale. New Haven, Conn, Yale Medical School, 1989
22. Lowy MT: Quantification of type I and II adrenal steroid receptors in neuronal, lymphoid, and pituitary tissues. Brain Res 1989; 503:191–197
23. Schlechte JA, Sherman B: Lymphocyte glucocorticoid receptor binding in depressed patients with hypercortisolemia. Psychoneuroendocrinology 1985; 10:469–474
24. Kontula K, Andersson LC, Huttunen M, et al: Reduced level of cellular glucocorticoid receptors in patients with anorexia nervosa. Horm Metab Res 1982; 14:619–620
25. Svec F: Glucocorticoid receptor regulation. Life Sci 1985; 36: 2359–2366
26. Turner BB: Tissue differences in the up-regulation of glucocorticoid-binding proteins in the rat. Endocrinology 1986; 118: 1211–1216
27. Bloomfield CD, Smith KA, Peterson BA, et al: In vitro glucocorticoid studies in human lymphoma: clinical and biological significance. J Steroid Biochem 1981; 18:275–284
28. Kontula K, Pelkonen R, Andersson L, et al: Glucocorticoid receptors in adrenocorticoid disorders. J Clin Endocrinol Metab 1980; 51:654
29. Junker K: Glucocorticoid receptors of human mononuclear leukocytes in vitro. J Clin Endocrinol Metab 1983; 57:506–512
30. LaCroix A, Bonnard GD, Lippman ME: Modulation of glucocorticoid receptors by mitogenic stimuli, glucocorticoids and retinoids in normal human cultured T cells. J Steroid Biochem 1984; 21:73–80
31. Lowy MT: Reserpine induced decrease in type I and II corticosteroid receptors in neuronal and lymphoid tissue of adrenalectomized rats. Neuroendocrinology 1990; 51:190–196
32. Meaney MJ, Aitken DH, vanBerkel C, et al: Effect of neonatal handling on age-related impairments associated with the hippocampus. Science 1988; 239:766–768