Relationships Between the Pituitary-Adrenal Hormones, Insulin, and Glucose in Middle-Aged Men: Moderating Influence of Psychosocial Stress

Liisa Keltikangas-Järvinen, Niklas Ravaja, Katri Räikkönen, Aarno Hautanen, and Herman Adlercreutz

We examined whether the relationships between the pituitary-adrenal hormones (corticotropin [ACTH] and cortisol), insulin, and glucose differ as a function of psychosocial stress defined in terms of vital exhaustion (VE) and depressive behavior (DB). The participants were 69 normotensive and 21 unmedicated borderline hypertensive (BH) middle-aged men whose work is stressful. Hormonal and metabolic variables were measured during an oral glucose tolerance test (OGTT), and the cortisol response to dexamethasone (DXM) suppression and intravenous ACTH stimulation was also measured. We found that the basal ACTH level during the OGTT was positively associated with the cortisol response to ACTH at 60 minutes, the fasting insulin level, and the insulin to glucose ratio among exhausted and high DB men, while the reverse was true for nonexhausted and low DB men. Also, a high cortisol response to ACTH, a low cortisol level during the OGTT, and a high ratio of these cortisol determinations (cortisol ratio) were associated with high fasting insulin and glucose levels, the summed insulin values, and the insulin to glucose ratio only among nonexhausted and low DB men; among exhausted and high DB men, these associations were less pronounced, absent, or in the opposite direction. The findings suggest that VE and DB have a moderating influence on the relationships among the hormonal and metabolic parameters studied. Psychosocial stress may affect the pituitary-adrenocortical system in complex ways, contributing thereby to insulin resistance, hyperinsulinemia, and coronary heart disease (CHD) risk.

PROSPECTIVE epidemiological studies have demonstrated that hyperinsulinemia is associated with coronary heart disease (CHD) incidence and mortality,[1-3] although the independent contribution of insulinemia per se to CHD risk is still a matter of debate. An insulin-resistant hyperinsulinemic state is also frequently associated with a cluster of abnormalities—glucose intolerance, arterial hypertension, and dyslipidemia—comprising the metabolic syndrome that is of utmost importance in the pathogenesis of non–insulin-dependent diabetes mellitus and CHD.[4]

An increased activity of the hypothalamic-pituitary-adrenocortical axis has been suggested to contribute significantly to insulin resistance and hyperinsulinemia.[5] Cortisol excess may produce pronounced insulin resistance by direct effects on the periphery or through a mediating influence on abdominal fat accumulation.[5] However, the relationship between various components of the pituitary-adrenal axis and insulin metabolism is more complicated. Hypocortisolism, apparently caused by hypothalamic or central adrenal insufficiency, has also been associated with various metabolic CHD risk factors,[6] Hautanen and Adlercreutz[6] found that basal cortisol levels during the oral glucose tolerance test (OGTT) correlated negatively but the cortisol response to corticotropin (ACTH) correlated positively with fasting insulin and the waist to hip ratio.

Given that the ACTH-releasing factor (CRF)-ACTH-cortisol axis is very sensitive to psychosocial stress, this axis has been suggested to play an important role in mediating the influence of psychosocial stress on insulin resistance, hyperinsulinemia, and CHD risk.[7] Increased activity in the pituitary-adrenocortical system with elevated secretion of cortisol follows stress in general and a "defeat" or "helplessness" reaction to uncontrollable stress in particular.[7,8] However, the relationship between stress and cortisol secretion is also complicated. First, although stress-related personality dimensions such as type A behavior and hostility have been associated in men with elevated cortisol levels across experimental periods,[9] greater cortisol reactivity to stressors,[10,11] and increased cortisol excretion during typical daily activities,[12] an inverse relationship between type A behavior and day and night concentrations of cortisol has also been reported in both sexes.[13] Second, a combination of anger-out (a tendency to express anger toward other persons or the environment) and vital exhaustion[14] (VE), characterized by (1) unusual fatigue and loss of energy, (2) increased irritability, and (3) feelings of demoralization, has been shown to be related to a high cortisol response to dexamethasone (DXM) suppression and intravenous ACTH stimulation,[15] which implies hypocortisolism.[6] Similarly, the chronic fatigue syndrome is characterized by hypocortisolism, not hypercortisolism,[16] although null findings also exist.[17]

Together, the aforementioned lines of evidence suggest that the contradictory findings for the relationship between secretion of hormones along the hypothalamic-pituitary-adrenocortical axis and insulin and glucose metabolism might be accounted for by the intensity and chronicity of psychosocial stress an individual has experienced. That is, this relationship might differ as a function of experienced psychosocial stress. However, we know of no prior studies addressing this issue. Therefore, the aim of the present study was to examine the potential moderating influence of psychosocial stress, defined in terms of VE and depressive behavior (DB), on the relationships among the pituitary-adrenal hormones, insulin, and glucose in middle-aged men.

SUBJECTS AND METHODS

Sample

This study is a part of a research project to examine the hypothetical associations between various psychological and behavioral characteristics, neuroendocrine responses, and the insulin resistance syndrome. Several large commercial companies, trade unions, and sports clubs around the metropolitan area were notified about the study, and their

From the Departments of Psychology and Clinical Chemistry, University of Helsinki, Helsinki, Finland.

Submitted August 16, 1997; accepted June 5, 1998.

Address reprint requests to Niklas Ravaja, PhD, Department of Psychology, PO Box 4, FIN-00014 University of Helsinki, Finland.

0026-0495/98/4712-0003$03.00/0

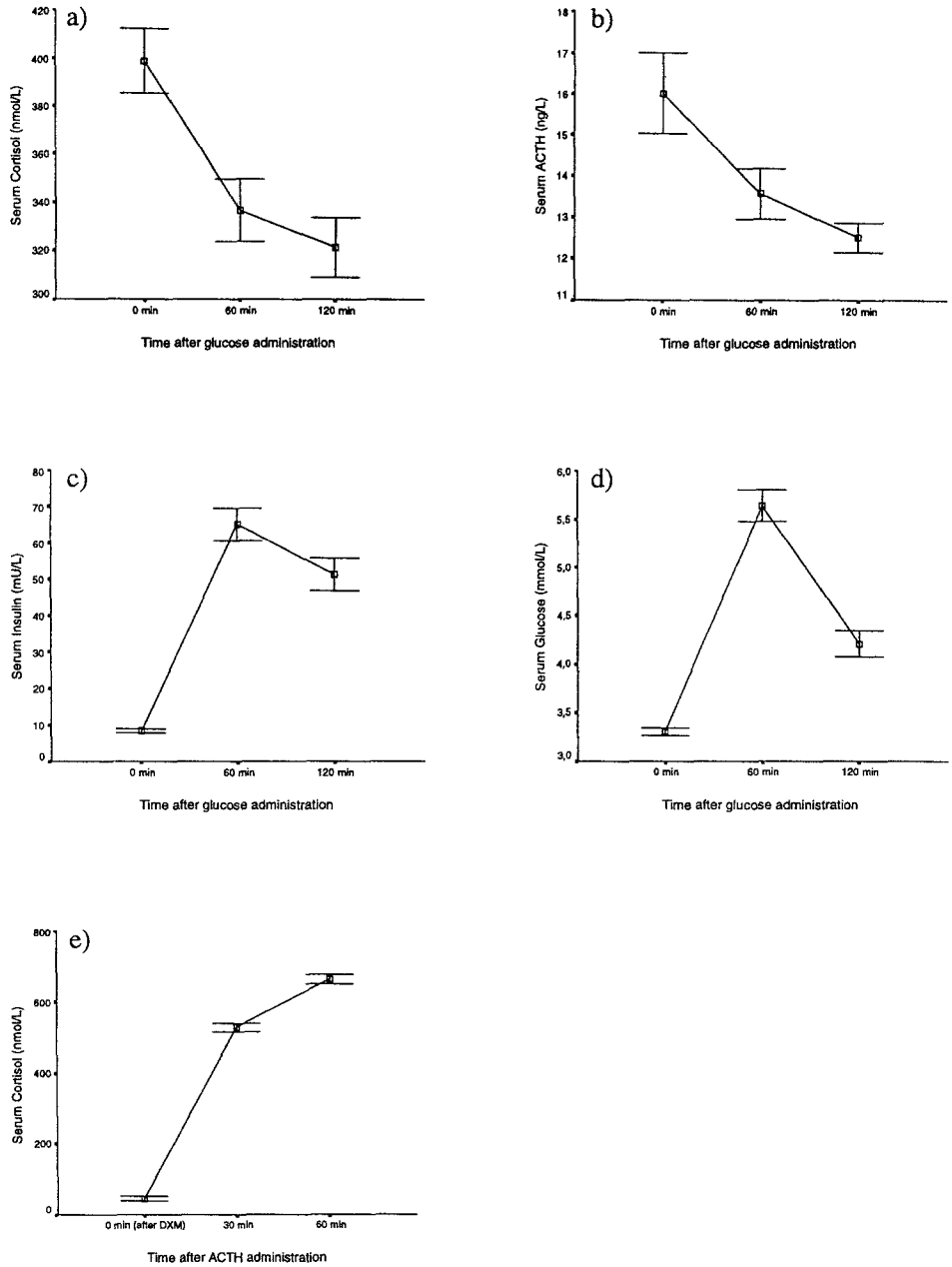

Fig 1. Mean ± SEM (a) cortisol, (b) ACTH, (c) insulin, and (d) glucose response during OGTT and (e) cortisol response to DXM suppression and ACTH stimulation in the study group (N = 90).

members were asked to participate voluntarily. Middle-aged men working as managers with many subordinates and with varying levels of education were eligible. Potential subjects were motivated to participate with a promise of an analysis of their all-around health status. Altogether, 101 men agreed to participate.

Of 101 men, 11 were excluded from the present study because of renovascular hypertension (n = 1), familial hypercholesterolemia (n = 1), non–insulin-dependent diabetes mellitus (n = 1), CHD (n = 4), and incomplete psychological data (n = 4). Thus, the subjects of the present study were 69 healthy normotensive and 21 unmedicated borderline hypertensive ([BH] blood pressure, 140/90 to 160/95 mm Hg) men aged 30 to 55 years (mean ± SD, 44.5 ± 5.4). They were receiving no medication and had no history or clinical evidence of liver, kidney, gastrointestinal, endocrine, inflammatory, or atherothrombotic disease or acute infection as determined by clinical examination and laboratory analyses.[15]

Measures

VE. VE was measured with Form B of the Maastricht Questionnaire[18] (MQ), a 21-item self-report measure. Instead of the original "yes/no" response format, each item was rated on a five-point scale from 1 (very strongly disagree) to 5 (very strongly agree). The VE score is the total of 21 items. Development of the original Form B of the MQ and its reliability and criterion validity is described in detail by Appels[18] and Appels et al.[14] Cronbach's α for the MQ was .88 for the present sample.

DB. DB was measured by a shortened 28-item version of the Depressive Behavior Survey Schedule (DBSS), a self-administered questionnaire by Cautela.[19] Each item was rated on a five-point scale from 1 (never holds true) to 5 (always holds true). The prevalence of depressive disorders appears to be relatively low in a normal population, and thus the distribution of depressive symptomatology in a

Table 1. Mean Values for Hormonal and Metabolic Variables in Normotensive and Borderline Hypertensive Men

Variable	Mean ± SD	Range
Normotensives (n = 69)		
Basal ACTH sum (ng/L)	41.8 ± 11.8	25.0-79.0
Cortisol (nmol/L)		
Sum	1,033 ± 253	490-2,106
Net response	1,113 ± 199	693-1,693
Net increment	604 ± 111	335-934
Insulin (mU/L)		
Fasting	7.2 ± 5.4	2.0-31.0
Sum	110.9 ± 74.4	22.0-374.0
Glucose (mmol/L)		
Fasting	3.2 ± 0.4	2.1-4.0
Sum	12.4 ± 2.1	7.3-18.6
BMI (kg/m²)	25.2 ± 3.3	20.1-35.1
Borderline hypertensives (n = 21)		
Basal ACTH sum (ng/L)	43.2 ± 24.6	26.0-143.0
Cortisol (nmol/L)		
Sum	1,136 ± 451	673-2,566
Net response	1,265 ± 251	734-1,662
Net increment	672 ± 151	427-906
Insulin (mU/L)		
Fasting	12.7 ± 7.1	4.0-27.0
Sum	171.4 ± 84.4	54.0-410.0
Glucose (mmol/L)		
Fasting	3.5 ± 0.4	2.7-4.5
Sum	15.6 ± 3.1	11.5-19.9
BMI (kg/m²)	29.5 ± 4.4	23.5-39.1

NOTE. Sum refers to the sum of 3 values measured at 0, 60, and 120 minutes during the OGTT. Net cortisol response is the sum of cortisol values at 30 and 60 minutes after ACTH stimulation minus DXM-suppressed cortisol level. Net increment of cortisol is the cortisol value at 60 minutes after ACTH stimulation minus DXM-suppressed cortisol level.

sample of healthy individuals is expected to be skewed. Therefore, we chose the DBSS, given that it includes many items to assess relatively mild forms of depression. For the same reason, items reflecting the most extreme form of depression (eg, "I feel like killing myself," or "I wish I were dead") were excluded from the original 43-item version of the DBSS. Thus, it should be recognized that the shortened version of the DBSS assesses depressive features in the normal range of personality rather than clinical depression. Cronbach's α for the shortened version of the DBSS was .92 for the present sample.

Although the correlation between the MQ and DBSS was high ($r = .75$, $P < .001$), only 57% of the subjects scoring in the top quartile (Q4) on the MQ also scored in the top quartile on the DBSS. Thus, although both the MQ and DBSS were used to measure the broad concept of psychosocial stress, they assess slightly different behavioral phenomena.

Hormonal and metabolic variables. ACTH, cortisol, insulin, and glucose values were measured on 2 consecutive days at the Helsinki University Central Hospital. On the first day at 7:30 AM, an OGTT was performed. An indwelling cannula was inserted into an antecubital vein; after 30 minutes, a standard load of 75 g glucose was given. Blood samples were drawn through the cannula at 0, 60, and 120 minutes after the glucose dose for determination of ACTH, cortisol, insulin, and glucose.

To measure the cortisol response of the adrenals to ACTH stimulation, the standard low-dose DXM suppression test was performed. On the first day at 11:00 PM, each subject received 1 mg DXM orally. Following DXM suppression, the secretory responsiveness of the adrenal cortex was measured by stimulation with exogenous ACTH. On the second day at 7:30 AM, an antecubital vein was cannulated; after 30 minutes, 10 μg/m² ACTH was injected intravenously. Blood was sampled at −30, 0, 30, and 60 minutes after administration of ACTH for determination of the serum cortisol concentration. All blood samples were collected after a 12-hour fast.

Commercial radioimmunoassay (RIA) kits were used for determination of serum cortisol (Farmos Diagnostica, Oulu, Finland) and insulin (Pharmacia, Uppsala, Sweden). Intact serum ACTH was determined by procedure A of the double-antibody RIA (Incstar, Stillwater, MN). The mean value of duplicate determinations was used in all calculations. High- and low-value quality-control samples were included in each assay. Samples were reanalyzed if the duplicate values differed by more than 10% from the calculated mean. The within- and between-assay imprecision (coefficient of variation [CV]) of the RIA methods, respectively, was as follows: cortisol, 6.4% and 7.0%; insulin, 5.1% and 7.5%. For ACTH, within- and between-assay CVs were, respectively, 3.4% and 23.1% (low control values) to 4.2% and 7.1% (high control

Table 2. Pearson Correlation Coefficients Among Hormonal, Metabolic, and Psychological Variables (N = 90)

Variable	1	2	3	4	5	6	7	8	9	10	11	12
1. Basal ACTH sum												
2. Basal cortisol sum	.31†											
3. Cortisol response to ACTH at 60 minutes	−.09	.24*										
4. Net cortisol response	−.20	.18	.95†									
5. Net increment of cortisol	−.28†	.08	.89†	.93†								
6. Cortisol ratio	−.38†	−.73†	.44†	.51†	.54†							
7. Fasting insulin	−.08	−.25*	.35†	.34†	.34†	.47†						
8. Insulin sum	−.13	−.23*	.32†	.30†	.30†	.42†	.80†					
9. Fasting glucose	−.06	.00	.12	.13	.16	.09	.30†	.30†				
10. Insulin to glucose ratio (fasting)	−.07	−.26*	.34†	.33†	.32†	.47†	.98†	.78†	.13			
11. Insulin to glucose ratio (sum)	−.14	−.24*	.29†	.27*	.27*	.40†	.80†	.95†	.17	.80†		
12. DB	.09	.25*	.00	−.05	−.05	−.26*	−.08	.02	−.08	−.07	.05	
13. VE	−.04	.20	.12	.10	.10	−.14	.12	.18	−.03	.13	.24*	.75†

NOTE. Sum refers to the sum of 3 values measured at 0, 60, and 120 minutes during the OGTT. Net cortisol response is the sum of cortisol values at 30 and 60 minutes after ACTH stimulation minus DXM-suppressed cortisol level. Net increment of cortisol is the cortisol value at 60 minutes after ACTH stimulation minus DXM-suppressed cortisol level. Cortisol ratio is the ratio of net cortisol response to basal cortisol sum during the OGTT. Logarithmic transformation was performed for all variables, with the exception of cortisol ratio, DB, and VE.

*$P < .05$.

†$P < .01$.

values). Blood glucose was measured using the glucose oxidase method.

Statistical Analyses

In the statistical analyses, we used the following parameters: (1) fasting insulin and glucose values; (2) in the OGTT, the sum of three measured values (0, 60, and 120 minutes) for ACTH, cortisol, and insulin as overall indicators of ACTH and cortisol secretion and insulinemia, respectively; (3) the net cortisol response (the sum of cortisol values at 30 and 60 minutes after ACTH stimulation minus the DXM-suppressed cortisol level at 0 minutes); (4) the net increment of cortisol (value from the DXM-suppressed level to poststimulation level 60 minutes after ACTH injection) used as a measure of the functional activity of the adrenals to ACTH stimulation; (5) the cortisol ratio (the ratio of net cortisol response to basal cortisol sum during the OGTT); and (6) an insulin to glucose ratio computed for the fasting levels and for the sum of the three measured values to additionally reflect insulin sensitivity.

The most frequently recommended approach to assess the moderator influences of a variable is moderated regression analysis involving a predictor variable, a moderator variable, and a product term.[20-22] Thus, the question of whether stress defined in terms of VE and DB has a moderating effect on the association of the pituitary-adrenal hormones with insulin and glucose was investigated by moderated regression analyses. Separate hierarchical regressions were performed for each of the dependent variables (eg, fasting insulin). The independent variables were entered in four steps in the following order: (1) age, (2) predictor variable (eg, basal cortisol sum), (3) moderator variable (VE or DB), and (4) predictor × moderator interaction term. Variables forming the product terms were centered to reduce possible multicollinearity among the independent variables.[20] Following the recommendations of Aiken and West,[20] significant interactions were graphed showing the regression lines for subjects receiving low (1 SD below the mean) and high (1 SD above the mean) scores on the measure of stress (VE or DB). Hormonal and metabolic variables (with the exception of the cortisol ratio) were logarithmically transformed before computing because of their skewed distribution. All analyses were performed in the whole sample and then repeated after excluding BH men and subjects reporting an ethanol intake greater than 400 g/wk (n = 5), because excessive drinking may alter cortisol secretion.[23]

RESULTS

Figure 1 shows the mean cortisol, ACTH, insulin, and glucose response during the OGTT and the cortisol response to DXM suppression and ACTH stimulation in the study population. Mean values for hormonal and metabolic variables in normotensive and BH men are also presented in Table 1. Table 2 shows intercorrelations of the hormonal, metabolic, and psychological variables. DB was positively and significantly correlated with the basal cortisol sum and negatively correlated with the cortisol ratio ($P < .05$). In addition, VE was positively and significantly associated with the insulin sum to glucose sum ratio ($P < .05$).

The results of moderated regression analyses with VE as the moderator variable are shown in Table 3. Statistically significant interactions are also depicted in Fig 2. Moderated regression analysis revealed a significant VE × basal ACTH sum interaction in predicting the cortisol response to ACTH at 60 minutes, fasting insulin, and the insulin to glucose ratio ($P = .012$, .026, and .043, respectively). That is, the basal ACTH sum was positively associated with the cortisol response to ACTH at 60 minutes, fasting insulin, and the insulin to glucose ratio in subjects with high VE scores, while the reverse was true for subjects with low VE scores. In addition, a significant VE × basal cortisol sum interaction was found for fasting insulin ($P = .015$); the basal cortisol sum was negatively related to insulin among subjects with low VE scores, while this association was virtually absent in subjects with high VE scores. A nearly identical VE × basal cortisol sum interaction emerged in predicting the insulin to glucose ratio ($P = .021$). When the analyses were repeated after excluding BH subjects and those reporting an ethanol intake greater than 400 g/wk, all of the aforementioned interactions failed to reach statistical significance ($P < .11$, but $P = .478$ for VE × basal ACTH sum interaction for the cortisol response to ACTH at 60 minutes). However, a significant VE × basal cortisol sum

Table 3. Interaction of VE With ACTH and Cortisol in Predicting Other Hormonal and Metabolic Parameters

Variable	β	R^2	Change in R^2	F	*df*
Whole sample (N = 90)					
Cortisol response to ACTH at 60 minutes					
Age	−.03		.003	0.28	1, 88
Basal ACTH sum	−.08		.009	0.78	1, 87
VE	.10		.013	1.13	1, 86
VE × basal ACTH sum	.27*	.096	.071	6.65*	1, 85
Fasting insulin					
Age	.03		.000	.000	1, 88
Basal ACTH sum	−.07		.006	0.52	1, 87
VE	.11		.014	1.23	1, 86
VE × basal ACTH sum	.24*	.075	.056	5.10*	1, 85
Insulin to glucose ratio (fasting)					
Age	.01		.000	0.04	1, 88
Basal ACTH sum	−.06		.005	0.45	1, 87
VE	.12		.016	1.40	1, 86
VE × basal ACTH sum	.22*	.068	.046	4.22*	1, 85
Fasting insulin					
Age	−.03		.000	0.00	1, 88
Basal cortisol sum	−.30†		.062	5.75†	1, 87
VE	.19		.030	2.84	1, 86
VE × basal cortisol sum	.25*	.154	.062	6.21*	1, 85
Insulin to glucose ratio (fasting)					
Age	−.05		.000	0.04	1, 898
Basal cortisol sum	−.32†		.069	6.44*	1, 87
VE	.20		.034	3.24	1, 86
VE × basal cortisol sum	.23*	.158	.054	5.49*	1, 85
Non–heavy-drinking normotensives (N = 64)					
Insulin sum					
Age	.05		.010	0.62	1, 62
Basal cortisol sum	−.20		.072	4.77	1, 61
VE	.37†		.096	7.02†	1, 60
VE × basal cortisol sum	.27*	.237	.059	4.56*	1, 59

NOTE. Sum refers to the sum of 3 values measured at 0, 60, and 120 minutes during the OGTT. Logarithmic transformation was performed for all variables, with the exception of VE. β coefficients were computed at the final step of each analysis. Only statistically significant findings are reported.

*$P < .05$.

†$P < .01$.

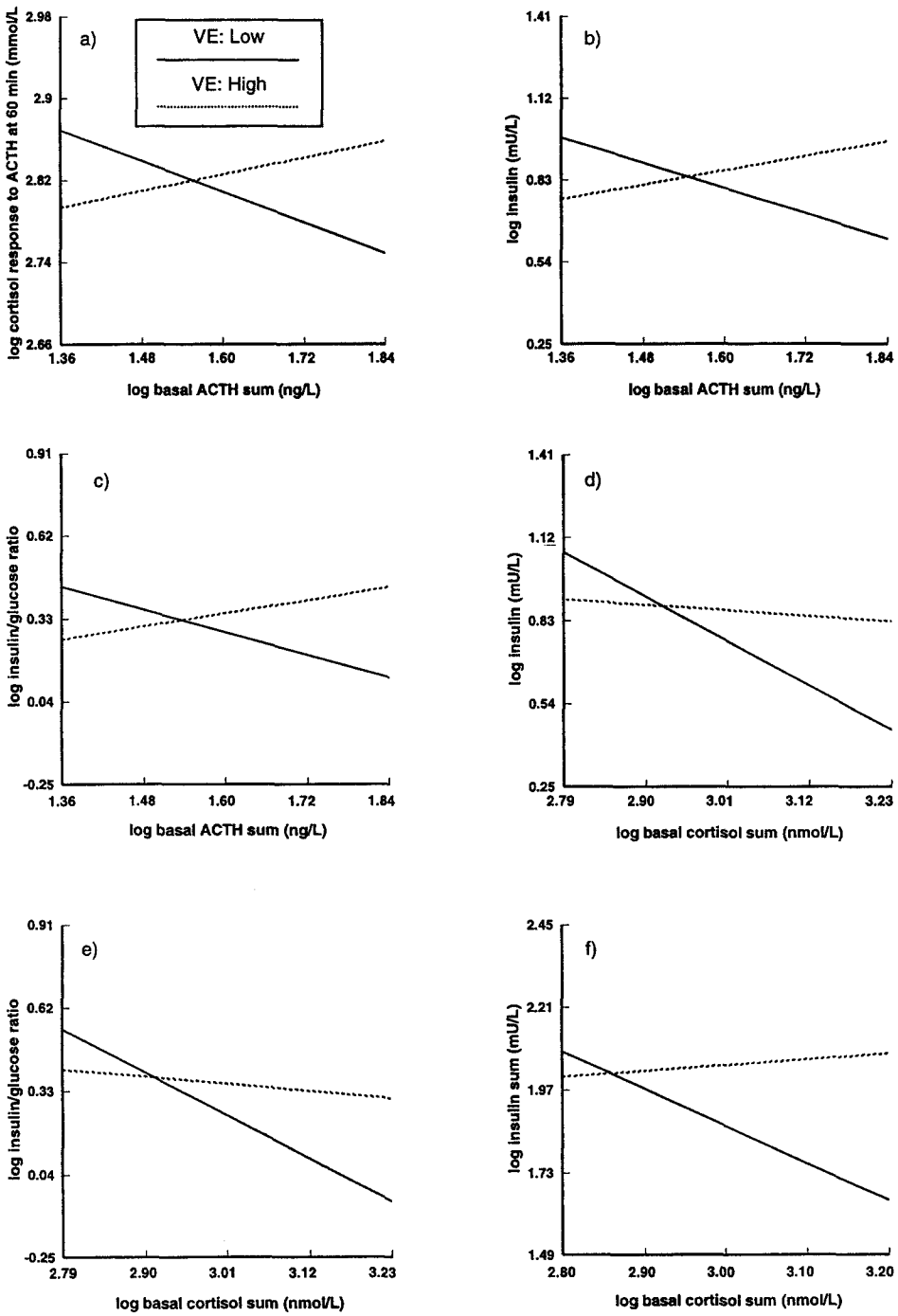

Fig 2. Relationships among the pituitary-adrenal hormones, insulin, and glucose in nonexhausted and exhausted men (range of the scale on x- and y-axes, mean ± 2 SD). (a-e) Analyses performed for the whole sample (N = 90); (f) analysis performed in non–heavy-drinking (reported ethanol intake <401 g/wk) normotensives (N = 64).

interaction emerged in predicting the summed insulin ($P = .037$). The basal cortisol sum was positively and weakly associated with the insulin sum among high-VE individuals, whereas there was a negative relationship between the two among individuals with low VE scores.*

The results of moderated regression analyses with DB as the moderator variable are shown in Table 4. In the whole sample, when regression analyses were performed using DB in lieu of VE as a moderator variable, three interactions similar to those found when VE served as a moderator variable emerged. A significant DB × basal ACTH sum interaction emerged in

*We repeated all moderated regression analyses after adjusting for the body mass index (BMI). In the whole sample, the VE × basal ACTH sum interaction for the cortisol response to ACTH at 60 minutes remained significant even after adjustment for BMI ($\beta = .21$, $P = .049$, R^2 change = .040). All other interactions failed to reach statistical significance. However, among non–heavy-drinking normotensives, VE remained a significant predictor of summed insulin after adjusting for BMI ($\beta = .32$, $P = .005$, R^2 change = .079).

Table 4. Interaction of DB With ACTH and Cortisol in Predicting Other Hormonal and Metabolic Parameters

Variable	β	R^2	Change in R^2	F	*df*
Whole sample (N = 90)					
Cortisol response to ACTH at 60 minutes					
Age	−.07		.003	0.28	1, 88
Basal ACTH sum	−.17		.009	0.78	1, 87
DB	.00		.000	0.00	1, 86
DB × basal ACTH sum	.28†	.087	.075	6.95†	1, 85
Fasting insulin					
Age	−.05		.000	0.00	1, 88
Basal cortisol sum	−.29†		.062	5.75*	1, 87
DB	−.03		.000	0.03	1, 86
DB × basal cortisol sum	.25*	.123	.061	5.91*	1, 85
Insulin to glucose ratio (fasting)					
Age	−.07		.000	0.04	1, 88
Basal cortisol sum	−.30†		.069	6.44*	1, 87
DB	−.01		.000	0.00	1, 86
DB × basal cortisol sum	.23*	.119	.050	4.79*	1, 85
Fasting glucose					
Age	.12		.014	1.25	1, 88
Net increment of cortisol	.17		.028	2.55	1, 87
DB	−.08		.004	0.39	1, 86
DB × net increment of cortisol	−.26*	.112	.065	6.24*	1, 85
Fasting glucose					
Age	.10		.014	1.25	1, 88
Cortisol ratio	.03		.007	0.62	1, 87
DB	−.08		.003	0.28	1, 86
DB × cortisol ratio	−.23*	.076	.052	4.80*	1, 85
Non–heavy-drinking normotensives (N = 64)					
Fasting glucose					
Age	.13		.019	1.19	1, 62
Net increme t of cortisol	.13		.009	0.57	1, 61
DB	−.01		.004	0.23	1, 60
DB × net increment of cortisol	−.29*	.108	.077	5.08*	1, 59
Fasting glucose					
Age	.15		.019	1.19	1, 62
Net cortisol response	.11		.007	0.42	1, 61
DB	.00		.004	0.25	1, 60
DB × net cortisol response	−.26*	.094	.065	4.20*	1, 59
Insulin sum					
Age	.06		.010	0.62	1, 62
Cortisol ratio	.47‡		.215	16.94‡	1, 62
DB	.20		.057	4.74*	1, 60
DB × cortisol ratio	−.24*	.336	.054	4.83*	1, 59
Insulin sum to glucose sum ratio					
Age	.05		.009	0.55	1, 62
Cortisol ratio	.45‡		.201	15.54‡	1, 61
DB	.20		.054	4.44*	1, 60
DB × cortisol ratio	−.22*	.312	.048	4.11*	1, 59

NOTE. Sum refers to the sum of 3 values measured at 0, 60, and 120 minutes during the OGTT. Net cortisol response is the sum of cortisol values at 30 and 60 minutes after ACTH stimulation minus DXM-suppressed cortisol level. Net increment of cortisol is the cortisol value at 60 minutes after ACTH stimulation minus DXM-suppressed cortisol level. Cortisol ratio is the ratio of net cortisol response to basal cortisol sum during the OGTT.Logarithmic transformation was performed for all variables, with the exception of cortisol ratio and DB. β coefficients were computed at the final step of each analysis. Only statistically significant findings are reported.

*$P < .05$.

†$P < .01$.

‡$P < .001$.

predicting the cortisol response to ACTH at 60 minutes ($P = .010$); the basal ACTH sum was positively related to the cortisol response to ACTH at 60 minutes in high-DB subjects, while the reverse was true for subjects with low DB scores. There was also a significant interaction between DB and the basal cortisol sum in predicting both fasting insulin and the insulin to glucose ratio ($P = .017$ and .031, respectively). The negative association of the basal cortisol sum with insulin and the insulin to glucose ratio was stronger among low-DB subjects compared with high-DB subjects. In addition, when

predicting fasting glucose, significant DB × net increment of cortisol and DB × cortisol ratio (ratio of net cortisol response to cortisol sum) interactions emerged ($P = .014$ and .031, respectively). The net increment of cortisol and the cortisol ratio were positively associated with glucose among subjects with low DB scores, while the reverse was true for men with high DB scores. The aforementioned statistically significant interactions are also depicted in Fig 3.

When these analyses were repeated after excluding BH men and those reporting an ethanol intake greater than 400 g/wk, the DB × net increment of cortisol interaction for fasting glucose remained significant ($P = .028$). All other aforementioned interactions failed to reach significance ($P < .09$, but $P = .773$ for the DB × basal ACTH sum interaction for the cortisol response to ACTH at 60 minutes). Moderated regression analysis showed three additional significant interactions. A significant DB × net cortisol response interaction emerged in predicting fasting glucose ($P = .045$); the net cortisol response was negatively associated with glucose among high-DB men, while the reverse was true for low-DB men. A significant DB × cortisol ratio interaction was also found in predicting both the insulin sum and the insulin sum to glucose sum ratio ($P = .032$ and .047, respectively). The positive associations between the cortisol ratio and summed insulin and between the cortisol ratio and the insulin sum to glucose sum ratio were stronger among low-DB scorers compared with high-DB scorers. These interactions are shown in Fig 4.†

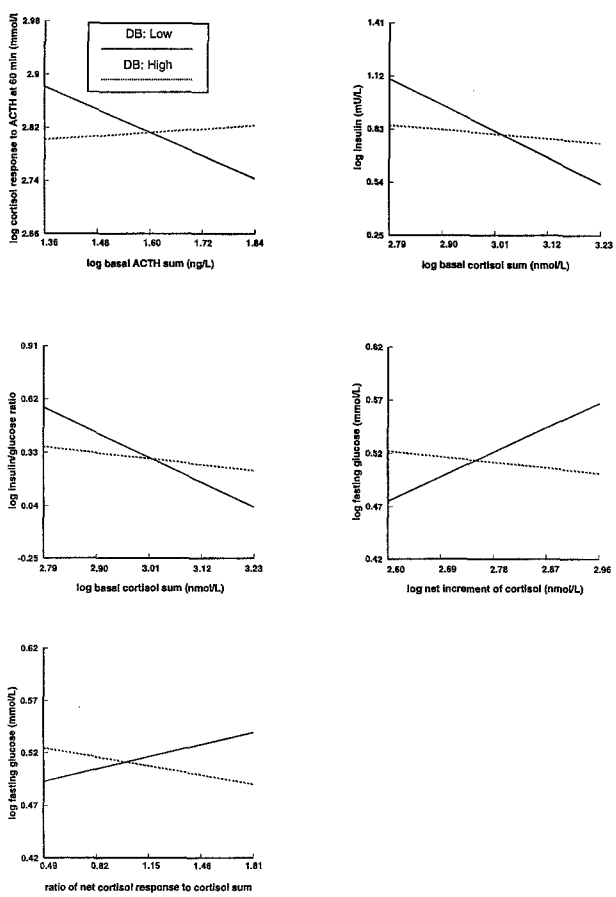

Fig 3. Relationships among the pituitary-adrenal hormones, insulin, and glucose in low-DB and high-DB men (range of the scale on x- and y-axes, mean ± 2 SD). Analyses were performed for the whole sample (N = 90).

DISCUSSION

The present study is the first to show that psychosocial stress defined in terms of VE and DB has a moderating influence on the relationships among the pituitary-adrenal hormones, insulin, and glucose in middle-aged men. We found that for exhausted (high-VE scorers) and high-DB men, basal ACTH levels during the OGTT were positively associated with the cortisol response to ACTH at 60 minutes, fasting insulin, and the insulin to glucose ratio. Conversely, for nonexhausted (low-VE scorers) and low-DB men, the basal ACTH sum was negatively related to the cortisol response to direct ACTH stimulation, fasting insulin, and the insulin to glucose ratio.

The reason for these divergent associations as a function of VE and DB is not readily apparent. However, an increased activity along the hypothalamic-pituitary-adrenal axis has been suggested as an early pathogenic factor for insulin resistance and hyperinsulinemia. Thus, psychosocial stress–induced increased sensitivity of the hypothalamic-pituitary-adrenocortical system may presumably account for the positive association of the basal ACTH level with the cortisol response to ACTH at 60 minutes, fasting insulin, and the insulin to glucose ratio among exhausted and high-DB individuals. At this time, the mechanisms underlying the negative relationship between the aforementioned hormonal and metabolic parameters among nonexhausted and low-DB men are unknown. However, it seems apparent that the negative relationship of the basal ACTH level with the cortisol response to ACTH at 60 minutes is based on a normal well-functioning feedback of cortisol on CRF release. Unfortunately, we did not examine the ability of CRF to increase ACTH release; this would have enabled determination of the sensitivity of the anterior pituitary to this influence (and provided an indication of the CRF-receptor interaction at the pituitary).

We also found that (1) basal cortisol levels were negatively related to fasting insulin and the insulin to glucose ratio in nonexhausted and low-DB men, while these associations were virtually absent in exhausted and high-DB men; (2) the ACTH-stimulated net cortisol response and net increment of

†When the moderated regression analyses were repeated after adjusting for BMI in the whole sample, the DB × basal ACTH sum interaction for the cortisol response to ACTH at 60 minutes remained significant ($\beta = .23$, $P = .032$, R^2 change = .048). Likewise, the DB × net increment of cortisol interaction remained significant in predicting fasting glucose ($\beta = -.26$, $P = .011$, R^2 change = .066). The DB × cortisol ratio interaction showed a similar nonsignificant tendency ($\beta = -.18$, $P = .099$, R^2 change = .028). Other interactions were also nonsignificant. As in the whole sample, among non–heavy-drinking normotensives, the DB × net increment of cortisol interaction remained significant in predicting fasting glucose when adjustment was made for BMI ($\beta = -.26$, $P = .040$, R^2change = .062). The DB × net cortisol response interaction for fasting glucose failed to reach significance ($\beta = -.24$, $P = .063$, R^2 change = .052). Other interactions were also nonsignificant. However, DB remained a significant predictor of the insulin sum to glucose sum ratio after adjusting for BMI ($\beta = .24$, $P = .033$, R^2 change = .068).

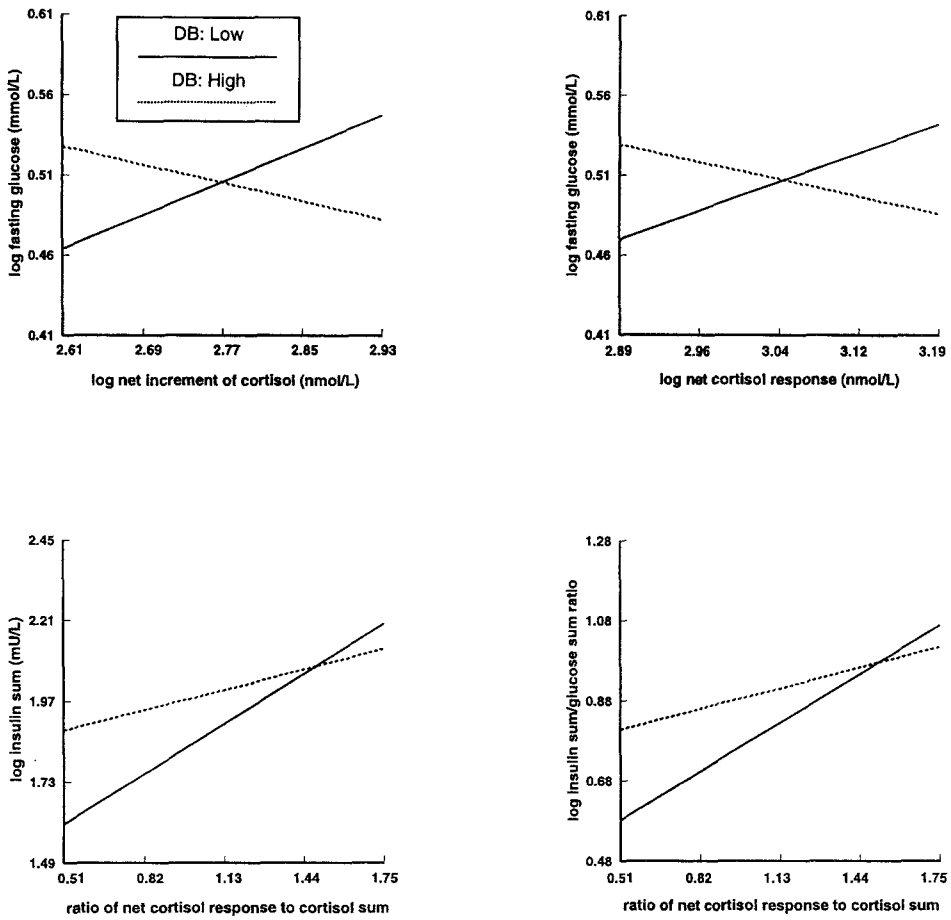

Fig 4. Relationships among the pituitary-adrenal hormones, insulin, and glucose in low-DB and high-DB men (range of the scale on x- and y-axes, mean ± 2 SD). Analyses were performed for non–heavy-drinking (reported ethanol intake <401 g/wk) normotensives (N = 64).

cortisol, as well as the cortisol ratio (ie, the ratio of net cortisol response to basal cortisol sum), were positively associated with fasting glucose among low-DB men, while the reverse was true for high-DB men; and (3) the positive associations between the cortisol ratio and summed insulin and between the cortisol ratio and the insulin sum to glucose sum ratio were stronger among low-DB compared with high-DB men. The cortisol ratio has previously been suggested as an index of central adrenal insufficiency.[6] However, in trying to understand the above-described associations, it is of note that the high cortisol response to ACTH stimulation may be due to several factors, including the following: (1) an increased adrenal cortisol reserve, for example, due to heightened ACTH stimulation (eg, Cushing's disease); (2) diminished cortisol reserve but possibly increased sensitivity of the adrenocortical receptors to ACTH stimulation (eg, central adrenal insufficiency, in which case the ACTH level should be low); and (3) adrenal hyperplasia, for example, due to a partial 21-hydroxylase defect.[24] In any case, the present findings indicate that the previously reported[6] negative association of the basal cortisol level and positive association of the cortisol response to ACTH and the cortisol ratio with fasting and summed insulin concentrations exists only among nonexhausted and low-DB men. By contrast, among exhausted and high-DB men, this association was less pronounced, absent, or in the opposite direction. It should be emphasized that the present results were generally very similar irrespective of whether VE or DB served as a moderator variable. Therefore, the divergence of the above-described relationships as a function of psychosocial stress is probably real.

The explanation for the divergent relationships of cortisol secretion to insulin and glucose is not readily apparent, either. In interpreting the findings, it is also of note that the observed differences in insulin and glucose concentrations may result from several factors, ie, changes in secretion of the hormones, changes in their ability to influence various body sites, changes in the associated synthetic or catabolic processes, or all of these. However, relevant to the association of a low cortisol level during the OGTT, a high cortisol response to ACTH, and a high cortisol ratio with high fasting insulin and glucose levels, summed insulin values, and the insulin to glucose ratio found among nonexhausted and low-DB individuals, there is evidence that (1) the peak cortisol response to CRF is diminished at higher circulating insulin levels[25] and (2) glucocorticoids and cortisol may inhibit insulin secretion,[26-28] and elevated levels of insulin may thereby result from a relative cortisol deficiency.[6] Obviously, exhaustion and DB mask the influences responsible for the negative association of the basal cortisol level and positive association of the cortisol response to ACTH and the cortisol ratio with insulin and glucose concentrations. Possibly relevant to this, insulin appears to interact with ACTH to modulate the secretion of cortisol. Kramer et al[29] showed that in the presence of low concentrations of ACTH, cortisol secretion was greater in the presence than in the absence of insulin; in

contrast, in the presence of a high concentration of ACTH, cortisol secretion was decreased at high insulin concentrations. In addition, depression, for example, has been shown to be associated with hypercortisolism,[30] and this appeared to be the case for DB also in the present study. The negative relationship for the net increment of cortisol and net cortisol response with fasting glucose found among high-DB men is, in effect, in line with the view that suggests an adverse influence of stress-induced hypercortisolism on insulin and glucose metabolism,[7] although fasting glucose per se is insufficient to permit firm conclusions about aberrations of insulin and glucose metabolism in individuals with fasting glucose values within the normal range. It is notable that although a combination of VE and anger-out has previously been shown to be related to a high net increment of cortisol,[15] such a behavioral constellation may differ, in particular, from DB in psychological significance and consequent neuroendocrine patterns. With the possible exception of the aforementioned associations and the weak positive relationship of basal cortisol levels with summed insulin values found among exhausted men, the present findings are not easily reconciled with evidence suggesting that the cortisol excess would cause insulin resistance and compensatory hyperinsulinemia. The relationships between various components of the pituitary-adrenal axis and insulin metabolism appear to be more complex.

Given that severe prolonged stress may ultimately result in diminished adrenal cortisol reserve,[15] it would also have been a reasonable expectation that the association of a low basal cortisol level and a high cortisol response to ACTH with a high insulin level and insulin to glucose ratio would exist particularly among exhausted individuals. However, although the present research participants were employed in obviously stressful managerial positions, it appears possible that the psychosocial stress they experienced was not prolonged and intense enough to result in diminished cortisol reserve. Of course, it remains possible that in another sample including individuals experiencing even more prolonged and pronounced stress, such severe stress would account, in part, for the possible association of hypocortisolemia with aberrations of insulin metabolism.

To summarize, these data shed light on the previous inconsistent findings by indicating that psychosocial stress, defined in terms of VE and DB, has a moderating influence on relationships between the hormones of the pituitary-adrenocortical system and insulin and glucose in middle-aged men. This influence might be predicated on the aforementioned interaction of insulin with ACTH to modulate cortisol secretion, for example. Apparently, psychosocial stress may affect the CRF-ACTH-cortisol axis in complex ways, thereby contributing to insulin resistance, hyperinsulinemia, and CHD risk. However, future studies should address the exact mechanisms underlying the divergent relationships among these hormonal and metabolic variables as a function of the high/low VE and high/low DB classifications.

REFERENCES

1. Després JP, Lamarche B, Mauriege P, et al: Hyperinsulinemia as an independent risk factor for ischemic heart disease. N Engl J Med 334:952-957, 1996
2. Welborn TA, Wearne K: Coronary heart disease incidence and cardiovascular mortality in Busselton with reference to glucose and insulin concentrations. Diabetes Care 2:154-160, 1979
3. Ducimetière P, Eschwège E, Papoz L, et al: Relationship of plasma insulin levels to the incidence of myocardial infarction and coronary heart disease mortality in a middle-aged population. Diabetologia 19:205-210, 1980
4. Reaven GM: Pathophysiology of insulin resistance in human disease. Physiol Rev 75:473-486, 1995
5. Björntorp P: Regional fat distribution—Implications for type II diabetes. Int J Obes 16:S19-S27, 1992 (suppl 4)
6. Hautanen A, Adlercreutz H: Altered adrenocorticotropin and cortisol secretion in abdominal obesity: Implications for the insulin resistance syndrome. J Intern Med 234:461-469, 1993
7. Björntorp P: Visceral fat accumulation: The missing link between psychosocial factors and cardiovascular disease? J Intern Med 230:195-201, 1991
8. Frankenhaeuser M: The psychophysiology of workload, stress, and health: Comparison between the sexes. Ann Behav Med 13:197-204, 1991
9. Williams RB, Suarez EC, Kuhn CM, et al: Biobehavioral basis of coronary-prone behavior in middle-aged men. I. Evidence for chronic SNS activation in type As. Psychosom Med 53:528-537, 1991
10. Williams RB, Lane JD, Kuhn CM, et al: Type A behavior and elevated physiological and neuroendocrine responses to cognitive tasks. Science 218:483-485, 1982
11. Lundberg U, Hedman M, Melin B, et al: Type A behavior in healthy males and females as related to physiological reactivity and blood lipids. Psychosom Med 51:113-122, 1989
12. Pope MK, Smith TW: Cortisol excretion in high and low cynically hostile men. Psychosom Med 53:386-392, 1991
13. Lambert WW, MacEvoy B, Klackenberg-Larsson I, et al: The relation of stress hormone excretion to type A behavior and to health. J Hum Stress 13:128-135, 1987
14. Appels A, Falger P, Schouten EGW: Vital exhaustion as risk indicator for myocardial infarction in women. J Psychosom Res 37:881-890, 1993
15. Keltikangas-Järvinen L, Räikkönen K, Hautanen A, et al: Vital exhaustion, anger expression, and pituitary and adrenocortical hormones. Implications for the insulin resistance syndrome. Arterioscler Thromb 16:275-280, 1996
16. Demitrack MA, Dale JK, Strauss SE, et al: Evidence for impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome. J Clin Endocrinol Metab 73:1224-1234, 1991
17. Hyyppä MT, Lindholm T, Lehtinen V, et al: Self-perceived fatigue and cortisol secretion in a community sample. J Psychosom Res 37:589-594, 1993
18. Appels A: Loss of control, vital exhaustion and coronary heart disease, in Steptoe A, Appels A (eds): Stress, Personal Control and Health. Brussels, Belgium, Wiley, 1989, pp 215-235
19. Cautela JR: Behavior Analysis Forms for Clinical Intervention. Champaign, IL, Research Press, 1979
20. Aiken LS, West SG: Multiple Regression: Testing and Interpreting Interactions. Newbury Park, CA, Sage, 1992
21. Baron RM, Kenny DA: The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. J Pers Soc Psychol 51:1173-1182, 1986
22. Cohen J, Cohen P: Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences (ed 2). Hillsdale, NJ, Erlbaum, 1983
23. Wand GS, Dobs AS: Alterations in the hypothalamic-pituitary-

adrenal axis in actively drinking alcoholics. J Clin Endocrinol Metab 72:1290-1295, 1991

24. Hautanen A, Adlercreutz H: Pituitary-adrenocortical function in abdominal obesity of males: Evidence for decreased 21-hydroxylase activity. J Steroid Biochem 58:123-133, 1996

25. Walker M, Berrish TS, James AR, et al: Effect of hyperinsulinemia on the function of the pituitary-adrenal axis in healthy man. Clin Endocrinol (Oxf) 40:493-497, 1994

26. Kalhan SC, Adam PA: Inhibitory effect of prednisone on insulin secretion in man: Model for duplication of blood glucose concentration. J Clin Endocrinol Metab 41:600-610, 1975

27. Van-Cauter E, Blackman JD, Roland D, et al: Modulation of glucose regulation and insulin secretion by circadian rhythmicity and sleep. J Clin Invest 88:934-942, 1991

28. Munck A, Guyre PM, Holbrook NJ: Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocr Rev 5:25-44, 1984

29. Kramer RE, Buster JE, Andersen RN: Differential modulation of ATCH-stimulated cortisol and androstenedione secretion by insulin. J Steroid Biochem 36:33-42, 1990

30. Ur E, Grossman A: Corticotropin-releasing hormone in health and disease: An update. Acta Endocrinol (Copenh) 127:193-199, 1992