Hypothalamic-Pituitary-Adrenal Axis and Sympathetic Nervous System Activities in Pima Indians and Caucasians

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It has been proposed that both hypercortisolism and low sympathetic nervous system (SNS) activity contribute to obesity. Because glucocorticoids inhibit SNS activity, we hypothesized that hypercortisolism and low SNS activity may be found in association in Pima Indians, a population with a high prevalence of obesity. We therefore measured indices of hypothalamic-pituitary-adrenal (HPA) axis and SNS activities in 39 nondiabetic men, 20 Pimas (age, 30 ± 5 years; weight, 94 ± 26 kg; 35% ± 8% body fat [mean ± SD]) and 19 Caucasians (33 ± 9 years, 91 ± 23 kg, 28% ± 11% body fat). HPA axis activity was assessed by measurements of morning fasting plasma corticotropin (ACTH) and cortisol concentrations and 24-hour urinary free cortisol (UFC) excretion. SNS activity was assessed as muscle sympathetic nerve activity (MSNA) by microneurography and by measurement of catecholamines (fasting plasma concentration and 24-hour urinary excretion). Plasma ACTH and cortisol and UFC were similar in Pimas and Caucasians. MSNA was positively correlated with percent body fat ($r = .49$, $P = .002$) and was lower in Pimas compared with Caucasians after adjustment for percent body fat (24 ± 9 *v* 31 ± 10 bursts/min, $P = .04$). We conclude that Pima Indians, a population with a high prevalence of obesity, have lower SNS activity but normal HPA axis activity compared with Caucasians.

GLUCOCORTICOIDS can promote preadipocyte differentiation,[1] increase lipoprotein lipase activity,[2] stimulate food intake,[3] and induce a moderate form of obesity with a characteristic regional fat accumulation.[4] However, unlike studies in animals,[5] human studies have indecisively proven the role of excessive hypothalamic-pituitary-adrenal (HPA) axis activity in the physiological control of adiposity.[6]

The HPA axis interacts complexly with the sympathetic nervous system (SNS) to maintain homeostasis during stress,[7] and there is evidence that glucocorticoids may play an inhibitory role on SNS activity.[8] Although plasma and urine catecholamines are in the normal range in individuals with Cushing's syndrome,[9,10] in both animals and humans, administration of glucocorticoids inhibits the activity of the SNS,[3,11-14] while adrenalectomy stimulates it.[15-17]

Pima Indians have the highest prevalence of diabetes and one of the highest prevalences of obesity in the world.[18] We have previously shown that Pimas have lower SNS activity compared with age- and weight-matched Caucasians.[19] Also, low systemic sympathoadrenal activity is associated with body weight gain and central adiposity in Pima Indians.[20] However, the underlying causes of the reduced SNS activity in Pima Indians are unknown.

We hypothesized that hypercortisolism may be associated with the low SNS activity observed in Pima Indians, and that increased HPA axis activity may contribute to the pathophysiology of obesity and diabetes in this population. To test this hypothesis, we studied HPA axis hormones (corticotropin [ACTH] and cortisol) and indices of SNS activity (muscle neuronal outflow and catecholamines) in Pima Indians and Caucasians.

SUBJECTS AND METHODS

Subjects

Twenty Pima Indian and 19 Caucasian males were admitted for 6 to 10 days to the metabolic ward of the Clinical Diabetes and Nutrition Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (Phoenix, AZ). Their physical characteristics are shown in Table 1. Women were not studied, to avoid the confounding effect of hormonal changes during the menstrual cycle. All subjects were in good health as determined from physical examination and routine blood and urine tests, and all had normal thyroid function. None were taking medications. Upon admission, subjects were placed on a weight-maintenance diet (50% carbohydrate, 30% fat, and 20% protein) calculated on the basis of body weight and adjusted to maintain body weight within ±1%. Sodium intake was 4 to 6 g/d depending on the weight-maintenance caloric requirement. Type 2 diabetes was excluded by an oral glucose tolerance test performed at least 3 days after admission. Body composition was assessed by dual-energy x-ray absorptiometry (DPX-1; Lunar, Madison, WI).[21] The circumference of the waist (at the level of the umbilicus) and thigh (at the gluteal fold) was measured supine and standing, respectively. The ratio of waist/thigh circumference (W/T ratio) was used as an estimate of body fat distribution.

The study was approved by the ethics committee of the National Institute of Diabetes and Digestive and Kidney Diseases and by the Tribal Council of the Gila River Indian Community. Subjects provided written informed consent.

Experimental Protocol

After at least 3 days of a weight-maintenance diet, two consecutive 24-hour urine collections were obtained for measurement of creatinine, free cortisol, and catecholamines and their metabolites. The first 24-hour urine collection was performed on a day spent in the ward with limited physical activity such as ambulation in the hallways, playing billiards and table tennis, and an optional supervised outing to a park adjacent to the hospital. The second 24-hour urine collection was performed on a day spent confined to a respiratory chamber.

On the following day after an overnight fast, muscle sympathetic nerve activity (MSNA) was measured by microneurography[19] and blood samples were collected over time for measurement of plasma glucose, insulin, ACTH, cortisol, and catecholamines and their metabo-

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Table 1. Characteristics of the Nondiabetic Male Subjects

Characteristic	Pima Indians (n = 20) Mean	Pima Indians (n = 20) Range	Caucasians (n = 19) Mean	Caucasians (n = 19) Range	P	All (n = 39)
Age (yr)	29	19-37	33	19-46	.091	31 ± 7
Height (cm)	172	164-185	178	165-188	.004	174 ± 7
Weight (kg)	94.2	60-148	91.4	58-156	.721	92.8 ± 24
Fat-free mass (kg)	59.7	44.1-80.6	63.7	51.5-77.6	.179	61.6 ± 9.3
Fat mass (kg)	34.5	14.3-68.2	27.7	3.9-80.3	.228	31.2 ± 17.6
Body fat (%)	35	21-52	28	5-51	.036	31 ± 10
W/T ratio	1.64	1.28-1.97	1.51	1.33-1.85	.020	1.58 ± 0.17
Fasting glucose (mg/dL)*	83	61-103	82	61-98	.911	82 ± 12
Fasting insulin (mU/mL)*†	17	6-33	9	4-15	.004	13 ± 8

*Measured in 17 Pima Indians and 13 Caucasians.

†Fasting plasma insulin was significantly correlated with percent body fat ($r = .61$, $P = .001$), and after adjustment for percent body fat, it was still significantly higher in Pimas ($P = .04$).

lites. Briefly, an intravenous plastic catheter was inserted in the antecubital vein at least 1 hour before the microneurography procedure and kept patent by saline infusion (<500 mL over 2 hours). Fifteen minutes and 1 minute before the start of the microneurography procedure, two blood samples were collected for baseline glucose and hormone measurements. Then, a tungsten microelectrode (200-μm shaft diameter, 1- to 5-μm noninsulated tip) was inserted into the peroneal nerve posterior to the fibular head. A reference electrode was inserted subcutaneously 1 to 3 cm from the recording electrode. The electrical signal was amplified, filtered, integrated, and recorded. MSNA was identified visually and expressed as the mean number of bursts per minute over a 20-minute period during which four more blood samples were collected (5 minutes apart) for glucose and hormone measurements.

Analytical Measurements

The plasma glucose concentration was measured by the glucose oxidase method (Beckman Glucose Analyzer; Beckman, Fullerton, CA), insulin by radioimmunoassay (Concept 4; ICN Biomedicals, Costa Mesa, CA), and free fatty acids by enzymatic microfluorimetry. Plasma ACTH and cortisol levels were measured by radioimmunoassay using a commercially available procedure. Plasma epinephrine, norepinephrine (NE), dihydroxyphenylalanine (DOPA), dihydroxyphenyl acetic acid (DOPAC), and dihydroxyphenylglycol (DHPG) and 24-hour urinary excretion of NE, dopamine, DOPA, DOPAC, and DHPG were measured by reversed-phase liquid chromatography with electrochemical detection.[22]

Statistical Analyses

All values are expressed as the mean ± SD unless otherwise indicated. Statistical analyses were performed using the procedures of the SAS Institute (Cary, NC). Plasma insulin concentrations were $\log_{10}$-transformed prior to parametric analysis to approximate a normal distribution. Since there was no significant change in plasma hormone concentrations before and after insertion of the microelectrode, results are presented as the mean of six plasma samples. Similarly, since no significant differences were observed in urinary hormone concentrations between the first and second day, results are presented as the mean of 2 days. Comparisons between MSNA/hormones and physical characteristics were assessed by Pearson's product-moment correlations. Using multiple regression analyses, MSNA was adjusted for percent body fat, urinary free cortisol (UFC) for body surface area (BSA) and 24-hour urinary creatinine, and urinary hormone excretion (catecholamines and metabolites) for 24-hour urinary creatinine (to account for completeness of urine collection and body [lean mass] size).

RESULTS

Physical characteristics of the subjects are shown in Table 1. Compared with Caucasians, Pima Indians were shorter and more obese (with a more centrally distributed adiposity) and had higher fasting plasma insulin.

HPA Axis

The fasting plasma ACTH concentration tended to be higher in Pimas than in Caucasians, whereas no difference in plasma cortisol was observed between the two groups (Table 2). No

Table 2. Fasting Plasma and 24-Hour Urine Hormone Concentrations in the Nondiabetic Male Subjects

Parameter	Pima Indians (n = 20) Mean	Pima Indians (n = 20) Range	Caucasians (n = 19) Mean	Caucasians (n = 19) Range	P	All (n = 39)
Fasting plasma hormone*						
ACTH (pg/mL)	27.8	9.4-51.5	21.9	7.6-40.2	.099	24.9 ± 11.3
Cortisol (μg/dL)	10.1	5.4-16.2	10.3	3.9-18.1	.854	10.2 ± 3.2
Epinephrine (pg/mL)	35.9	11.6-93.0	31.9	13-67.4	.522	33.9 ± 18.7
NE (pg/mL)	209.7	124.2-319.5	233.3	82.8-572.0	.475	221.2 ± 98.7
DOPA (pg/mL)	2,158	1,585-2,936	2,097	1,309-3,466	.728	2,128 ± 520
DOPAC (pg/mL)	1,268	1,009-1,947	1,668	929-2,474	.001	1,457 ± 398
DHPG (pg/mL)	1,014	836-1,190	1,040	724-1,658	.689	1,027 ± 199
24-hour urinary excretion rate†						
Creatinine (g/d)	1.38	0.70-2.90	1.68	0.85-2.40	.057	1.52 ± 0.50
UFC (μg/d)	83.7	36.7-181	85.5	38.2-138	.881	86.4 ± 36.4
NE (μg/d)‡	33.9	20.3-53.0	29.8	13.3-65.1	.317	32 ± 12
Dopamine (μg/d)‡	566	350-942	414	159-791	.018	490 ± 192
DOPA (μg/d)‡	71.2	21.6-124.7	53.8	17.8-89.8	.054	63 ± 26
DOPAC (μg/d)‡	790	259-1,229	876	318-1,457	.369	833 ± 275
DHPG (μg/d)‡	79.1	54.7-116.2	67.1	25.7-118.6	.073	73 ± 20

*Mean of 6 fasting plasma samples.

†Mean of 2 consecutive 24-hour urine collections.

‡Adjusted for 24-hour urinary creatinine excretion by linear regression analysis.

correlations were observed between these two hormones and anthropometric variables. Fasting plasma ACTH was positively correlated with fasting plasma cortisol in Caucasians ($r = .52$, $P = .02$), but not in Pimas ($r = .23$, $P = .32$).

Twenty-four-hour UFC excretion was similar in Pimas and Caucasians (Table 2 and Fig 1) and was positively correlated with BSA ($r = .39$, $P = .01$) and 24-hour urinary creatinine excretion ($r = .54$, $P = .001$). After adjustment for BSA (88.1 ± 34.9 *v* 84.7 ± 32.7 μg/d, $P = .76$) or urinary creatinine (93.0 ± 28.5 *v* 79.4 ± 32.1 μg/d, $P = .17$), 24-hour UFC excretion remained similar in Pimas and Caucasians. When expressed per unit of BSA, 24-hour UFC excretion was 41.2 ± 16.0 $\mu g/m^2 \cdot d^{-1}$ in Pimas and 42.1 ± 16.4 $\mu g/m^2 \cdot d^{-1}$ in Caucasians ($P = .86$).

Sympathoadrenal System

Expressed as an absolute value, MSNA was similar in Pimas and Caucasians (26 ± 12 *v* 29 ± 12 bursts/min, $P = .48$) and was positively correlated with the percent body fat ($r = .49$, $P = .002$) and W/T ratio ($r = .35$, $P = .04$). After adjustment for percent body fat, MSNA was not influenced by the W/T ratio and was lower in Pimas versus Caucasians (24 ± 9 *v* 31 ± 10 bursts/min, $P = .04$). Adjusted MSNA was positively correlated with fasting plasma NE ($r = .65$, $P = .001$) and DHPG ($r = .35$, $P = .03$) (Fig 2).

All fasting plasma catecholamine concentrations were similar in the two groups, except for the lower fasting plasma DOPAC in Pima Indians. The fasting plasma NE concentration was positively correlated with age ($r = .49$, $P = .002$). After adjustment for age, fasting plasma NE remained similar in Pimas and Caucasians.

Twenty-four-hour urinary excretion rates of NE and its metabolites were similar in Pimas and Caucasians. However, after adjustment for 24-hour urinary creatinine, 24-hour excretion rates of dopamine and DOPA were significantly higher in Pimas than in Caucasians (Table 2).

Correlations Between Sympathoadrenal System and HPA Axis

By multiple regression analysis, MSNA was found to be positively related to fasting plasma ACTH, but at each plasma ACTH concentration, Pima Indians had lower MSNA than Caucasians. Similarly, MSNA was found to be positively related to fasting plasma cortisol, but at each plasma cortisol concentration, Pima Indians had lower MSNA than Caucasians (Table 3). By the same multiple regression analyses, no significant interaction terms were found between indices of HPA axis activity (ACTH/cortisol) and race. In the entire group, adjusted 24-hour urinary NE was positively correlated with adjusted 24-hour UFC ($r = .48$, $P = .004$).

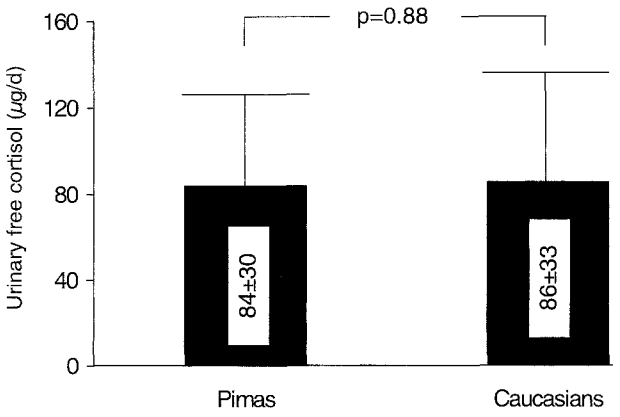

Fig 1. Twenty-four-hour UFC excretion rate in 20 nondiabetic Pima Indian (n = 20) and Caucasian (n = 19) males. When expressed per unit of BSA, 24-hour UFC excretion was 41.2 ± 16.0 $\mu g/m^2 \cdot d^{-1}$ in Pimas and 42.1 ± 16.4 $\mu g/m^2 \cdot d^{-1}$ in Caucasians ($P = .86$).

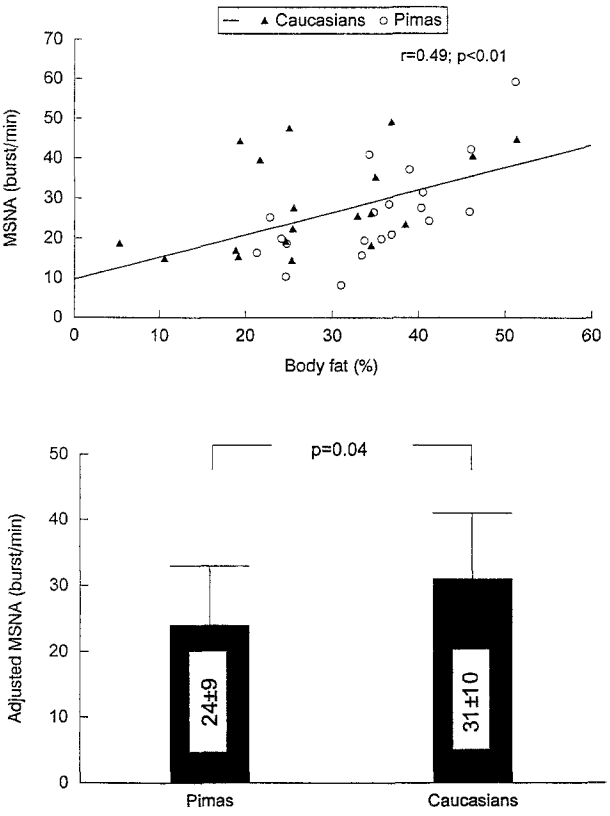

Fig 2. As an absolute value, MSNA was similar in 20 nondiabetic Pima Indian (n = 20) and Caucasian (n = 19) males and positively correlated with percent body fat. After adjustment for percent body fat, MSNA was significantly lower in Pimas than in Caucasians.

DISCUSSION

In the present study, we sought to evaluate whether hypercortisolism and low SNS activity are found in association in Pima Indians. We have confirmed that Pima Indians have lower SNS activity than Caucasians, and found this difference at each level of HPA axis activity. However, we did not find any difference in morning plasma ACTH and cortisol concentrations or 24-hour UFC excretion between Pimas and Caucasians. A positive correlation was observed between MSNA and plasma ACTH/cortisol concentrations. Although our findings seem to indicate that Pima Indians are not hypercortisolemic compared with Caucasians, we cannot exclude the possibility that the lower SNS activity in Pimas may result from a higher sensitivity of the SNS to the inhibitory effect of glucocorticoids.

The role of HPA axis activity in human obesity remains unclear.[6] However, forms of chronic hypercortisolism are

Table 3. Multiple Linear Regression Analysis of MSNA by Characteristics of Interest Including Indices of HPA Axis Activity (fasting plasma ACTH, model 1; fasting plasma cortisol, model 2)

Dependent Variable = MSNA (bursts/min)	Estimate (β)	SE	P
Model 1			
Intercept	−4.1193	6.8773	.5530
Body fat (%)	0.6400	0.1625	.0004
ACTH (pg/mL)	0.2798	0.1471	.0655
Race			
Pima Indian	—	—	—
Caucasian	8.8384	3.3978	.0135
Model 2			
Intercept	−8.3893	7.8725	.2939
Body fat (%)	0.6973	0.1597	.0001
Cortisol (μg/mL)	1.0001	0.4847	.0466
Race			
Pima Indian	—	—	—
Caucasian	7.3734	3.2936	.0316

associated with increased adiposity,[4] an effect that may be attributable to the stimulating effect of glucocorticoids on food intake.[3] Our data do not support a major role of the HPA axis in the etiology of obesity in Pima Indians.

It has recently been shown that cortisol measurements in the late evening are more likely to identify mild forms of hypercortisolism as compared with morning cortisolemia and/or 24-hour UFC excretion.[23] Therefore, we cannot exclude the possibility that we failed to detect subclinical differences in HPA axis activity between Pimas and Caucasians. Within the limitation imposed by the methodology used in the present study, we cannot confirm the hypothesis that the lower SNS activity observed in Pima Indians may be due to hypercortisolism.

However, we cannot exclude other possibilities. The interaction between the HPA and SNS is part of the adaptational response to stress.[24] The principal components of this response are corticotropin-releasing hormone ([CRH] controlling the HPA axis) and the noradrenergic neurons of several brainstem nuclei controlling the SNS.[25] Functionally, CRH and noradrenergic neurons participate in a positive central feedback loop that results in reciprocal activation.[26,27] Therefore, in the resting condition (or in the early phase of the stress response), the activity of the SNS parallels the activity of the HPA axis. This is compatible with our observations of a positive correlation between indices of SNS activity (MSNA and 24-hour urinary NE excretion rates) and indices of HPA axis activity (fasting plasma ACTH/cortisol and 24-hour UFC) in the resting condition.

However, the stress response is meant to be acute or at least of limited duration, given the long-term catabolic and immunosuppressive effects.[24] Glucocorticoids secreted by the adrenal glands in response to stress, exert an inhibitory feedback on both the HPA axis (via CRH and ACTH) and SNS (directly on noradrenergic neurons and indirectly via CRH),[24,28] thus limiting the stress response. This inhibitory effect is also observed in response to glucocorticoid administration.[3,11,13,14] Furthermore, it has been shown that glucocorticoids not only inhibit SNS activity in response to stress,[8] they also exert an inhibitory tonic control at rest.[29]

We found that at each level of HPA axis activity, Pima Indians seem to have lower levels of sympathetic nerve outflow than Caucasians. Although these findings do not prove causality, they are compatible with the hypothesis of a higher sensitivity of the SNS to the inhibitory tonic effect of glucocorticoids. In line with this hypothesis, we have recently observed in a pilot study that acute hypocortisolism induced by administration of metyrapone caused a larger increase in muscle SNS activity in two Pima Indians compared with two Caucasians, suggesting that Pimas may indeed be more sensitive to the inhibitory tone of glucocorticoids on the SNS.[30] Further studies are warranted to explore this possibility, especially after the recent observation that a polymorphism in the glucocorticoid receptor gene is associated with increased in vivo sensitivity to glucocorticoids, without signs of clinical hypercortisolism.[31] Whether the prevalence of this polymorphism is increased in Pima Indians is unknown.

The unexpected findings of this study are the lower plasma DOPAC concentration and the higher 24-hour urinary dopamine and DOPA excretion in Pima Indians compared with Caucasians. Although the lower plasma DOPAC concentration is compatible with the lower SNS activity observed in Pima Indians, and higher dopamine and DOPA urinary excretion rates have been reported to be associated with skin hyperpigmentation,[32] it is difficult to understand the physiological implication (if any) of these findings.

In conclusion, our results do not support the hypothesis that the lower SNS activity observed in Pima Indians may be due to hypercortisolism. However, we cannot exclude the possibility that the SNS of Pima Indians is more sensitive to the inhibitory effect of glucocorticoids. Longitudinal and/or interventional studies are warranted to further understand the interaction between the SNS and HPA axis in humans.

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REFERENCES

1. Hauner H, Schmid P, Pfeiffer EF: Glucocorticoid and insulin promote the differentiation of human adipocyte precursor cells into fat cells. J Clin Endocrinol Metab 64:832-835, 1987

2. Rebuffe-Scrive M, Krotkiewsky M, Elfverson J, et al: Muscle and adipose tissue morphology and metabolism in Cushing's syndrome. J Clin Endocrinol Metab 67:1122-1128, 1988

3. Tataranni PA, Larson DE, Snitker S, et al: The effects of glucocorticoids on energy metabolism and food intake in humans. Am J Physiol 271:E317-E325, 1996

4. Lamberts SW, Birkenhager JC: Body composition in Cushing's disease. J Clin Endocrinol Metab 42:864-868, 1976

5. York DA, Holt SJ, Allars J, et al: Glucocorticoids and the central control of sympathetic activity in the obese fa/fa rat, in Bjorntorp P, Rossner S (eds): Obesity in Europe 88. London, Lippey, UK, 1988, pp 247-252

6. Chalew S, Nagel H, Shore S: The hypothalamic-pituitary-adrenal axis in obesity. Obes Res 4:371-382, 1995

7. Munck A, Guyre PM, Holbrook NJ: Physiological functions of

glucocorticoids in stress and their relation to pharmacological actions. Endocr Rev 5:25-44, 1984

8. Kvetnansky R, Fukuhara K, Pacak K, et al: Endogenous glucocorticoids restrain catecholamine synthesis and release at rest and during immobilization stress in rats. Endocrinology 133:1411-1419, 1993

9. Ritchie CM, Sheridan B, Fraser R, et al: Studies on the pathogenesis of hypertension in Cushing's disease and acromegaly. Q J Med 280:855-867, 1990

10. Tenscher TW, Baumgart B, Greminger P, et al: Pathogenetic aspects of hypertension in Cushing's syndrome. Cardiology 72:184-190, 1985

11. Brown MR, Fisher LA: Glucocorticoid suppression of the sympathetic nervous system and adrenal medulla. Life Sci 39:1003-1012, 1986

12. Parvez H, Parvez S: Control of catecholamine release and degradation by the glucocorticoids. Experientia 28:1330-1332, 1972

13. Lenders JW, Golcynska A, Goldstein DS: Glucocorticoids, sympathetic activity, and presynaptic α_2-adrenoceptor function in humans. J Clin Endocrinol Metab 80:1804-1808, 1995

14. Randin D, Vollenweider P, Tappy L, et al: Suppression of alcohol-induced hypertension by dexamethasone. N Engl J Med 332:1733-1737, 1995

15. Parvez S, Parvez H, Roffi J: Hypophyseal-adrenocortical role in urinary excretion of epinephrine and norepinephrine in hypophysectomized and adrenalectomized rats. Endocrinology 94:1054-1059, 1974

16. Ismahan G, Parvez H, Parvez S, et al: Comparative effects of hypophysectomy and adrenalectomy upon plasma and adrenal monoamines in pregnant and non-pregnant rats. Br J Pharmacol 60:385-391, 1977

17. Von Euler US, Franksson C, Hellstrom J: Adrenaline and noradrenaline output in urine after unilateral and bilateral adrenalectomy in man. Acta Physiol Scand 31:1-5, 1954

18. Knowler WC, Pettitt DJ, Saad MF, et al: Obesity in the Pima Indians: Its magnitude and relationship with diabetes. Am J Clin Nutr 53:1543S-1551S, 1991 (suppl)

19. Spraul M, Ravussin E, Fontvieille AM, et al: Reduced sympathetic nervous activity. A potential mechanism predisposing to body weight gain. J Clin Invest 92:1730-1735, 1993

20. Tataranni PA, Young JB, Bogardus C, et al: A low sympathoadrenal activity is associated with body weight gain and development of central adiposity in Pima Indian men. Obes Res 5:341-347, 1997

21. Tataranni PA, Ravussin E: Use of dual-energy x-ray absorptiometry in obese individuals. Am J Clin Nutr 62:730-734, 1995

22. Cizza G, Pakac K, Kvetnansky R, et al: Decreased stress responsivity of central and peripheral catecholaminergic systems in aged 344/N Fisher rats. J Clin Invest 95:1217-1224, 1995

23. Papanicolau DA, Yanovski JA, Cutler GB, et al: A single midnight serum cortisol measurement distinguishes Cushing's syndrome from pseudo-Cushing states. J Clin Endocrinol Metab 83:1163-1167, 1998

24. Chrousos GP, Gold PW: The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. JAMA 267:1244-1252, 1992

25. Gold PW, Goodwin F, Chrousos GP: Clinical and biochemical manifestations of depression: Relationship to the neurobiology of stress. N Engl J Med 319: 348-420, 1988

26. Valentino RJ, Foote SL, Aston-Jones G: Corticotropin-releasing hormone activates noradrenergic neurons in locus coeruleus. Brain Res 270:363-367, 1983

27. Calogero AE, Gallucci WT, Chrousos GP, et al: Effect of the catecholamines upon rat hypothalamic corticotropin releasing hormone secretion in vitro: Clinical implications. J Clin Invest 82:839-846, 1988

28. Calogero A, Gallucci WT, Gold PW, et al: Multiple regulatory feedback loops on hypothalamic corticotropin releasing hormone secretion. J Clin Invest 82:767-774, 1988

29. Udelsman R, Goldstein DS, Loriaux DL, et al: Catecholamine-glucocorticoid interactions during surgical stress. J Surg Res 43:539-545, 1987

30. Cizza G, Tataranni PA, Lotsikas A, et al: Decreased muscle sympathetic activity and exaggerated inhibition by glucocorticoids in Pima Indians. Presented at the 80th Annual Meeting of the Endocrine Society, New Orleans, LA, June 24-27, 1998 (abstr)

31. Huizenga NATM, Koper JW, De Lange P, et al: A polymorphism of the glucocorticoid receptor gene may be associated with an increased sensitivity to glucocorticoids in vivo. J Clin Endocrinol Metab 83:144-151, 1998

32. Sowers JR, Zemel MB, Zemel P, et al: Salt sensitivity in Blacks. Salt intake and natriuretic substances. Hypertension 12:485-490, 1988