Anterior Pituitary and Pituitary-Dependent Target Organ Function in Men Infected With the Human Immunodeficiency Virus

L.D. Wilson, M.P.M. Truong, A.R. Barber, and T.T. Aoki

To evaluate pituitary and pituitary-dependent target organ function in men infected with the human immunodeficiency virus (HIV), 26 ambulatory HIV-positive men (13 with acquired immunodeficiency syndrome [AIDS]) and nine healthy control men were administered rapid sequential injections of thyrotropin (TSH)-releasing hormone (TRH), gonadotropin-releasing hormone (GnRH), ovine corticotropin (ACTH)-releasing hormone (oCRH), and human growth hormone-(GH)-releasing hormone (hGHRH). Blood samples were collected before and for 90 minutes after the injections for immunoassay of pituitary hormones, cortisol, testosterone, and free thyroxine (fT_4). Data were analyzed for each group of men considering basal, peak, and incremental responses to the releasing hormones, as well as the time course of response of each hormone. Mean basal serum GH concentrations were the same in all groups (control, AIDS, and non-AIDS HIV-positive), but stimulated GH levels were substantially higher at all time points in both groups of HIV-positive subjects. Results for prolactin (PRL) were similar, although stimulated PRL levels were increased significantly only in the AIDS group. The mean basal serum TSH concentration and stimulated TSH levels at 60 and 90 minutes were significantly greater in the AIDS group than in the control group. Basal mean fT_4 concentration in the AIDS group was significantly less than in the control group. Mean basal and stimulated serum (total) testosterone concentrations in all groups were the same. However, basal serum luteinizing hormone (LH) concentrations in both groups of HIV-infected men were significantly greater than in controls; stimulated (peak) LH levels were not different from control levels. Basal and peak stimulated plasma ACTH concentrations were significantly increased in both HIV-infected groups. Basal serum cortisol levels were also greater, on average, in HIV-infected groups, although stimulated (peak) cortisol responses were not different. These results indicate that basal serum concentrations of TSH, LH, ACTH, and cortisol are modestly increased in men with AIDS, and that maximum levels of GH, PRL, TSH, and ACTH stimulated by the releasing hormones are also increased in this group. Measurements obtained in the non-AIDS HIV-infected men showed a pattern generally similar to that obtained in men with AIDS, but less marked. The basis for the increased pituitary activity is unknown; we speculate that it is due to modestly impaired target organ function and to increased hypothalamic stimulation.

BECAUSE OF autopsy findings in patients with acquired immunodeficiency syndrome (AIDS) of necrosis and involvement of endocrine glands with opportunistic infections[1-8] and because of clinical features (weight loss, orthostatic hypotension, hyponatremia, decreased libido, etc.) suggesting endocrine abnormalities, there has been considerable interest in the endocrine status of patients infected with the human immunodeficiency virus (HIV).[9-11]

The frequency of frank adrenal insufficiency (both primary and secondary) in AIDS is increased, with 5% to 12% of patients showing inadequate cortisol responses to exogenous corticotropin (ACTH), whereas more subtle pituitary-adrenal abnormalities are much more frequent.[12-14] Approximately 30% to 50% of men with AIDS are reported to have decreased serum testosterone concentrations[13,15-17]; serum luteinizing hormone (LH) concentrations are reported to be inappropriately normal or decreased,[13,16] suggesting secondary (or tertiary) hypogonadism, but normal or increased LH concentrations have also been reported.[15,17-19] Clinically significant thyroid dysfunction appears to be uncommon[13,18,20-25] and evidently is not a significant contributor to the weight loss frequently observed in AIDS.[23] Generally, serum concentrations of total thyroxine (T_4), thyrotropin (TSH), and free T_4 are within normal limits, but contrary data exist.[19,24] Data regarding growth hormone (GH) secretion in patients infected with HIV are limited, although several examples of GH deficiency have been described.[26-28] Asymptomatic HIV-seropositive men and men with AIDS are reported to have normal serum prolactin (PRL) concentrations,[13,18,29] but elevated basal PRL concentrations (as well as increased LH and follicle-stimulating hormone [FSH] levels) in men with AIDS or AIDS-related complex (ARC) have also been reported.[15,19]

Clearly, there is no consistent picture of clinically significant endocrine abnormalities in patients infected with HIV. Nonetheless, there are examples of growth failure (presumably due to GH deficiency), hypogonadism, and adrenocortical insufficiency, and in many more instances there appear to be more subtle abnormalities of one or more hormonal systems. To avoid reliance on single measurements of serum hormones and to better assess the regulatory integrity of pituitary and pituitary-dependent target organs, we have elected to measure in HIV-infected men serum responses of multiple serum hormones to an acute infusion of the four known hypothalamic-releasing hormones.[30,31]

SUBJECTS AND METHODS

All subjects were ambulatory men recruited from an evening outpatient clinic limited to HIV-infected patients. A control group of nine healthy men of similar age without significant health problems were also studied. All received a brief physical examination, and a health history form was completed. Medical records

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Address reprint requests to L.D. Wilson, MD, Department of Medicine, Division of Endocrinology and Metabolism, FOLB II-C, University of California, Davis Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817.

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were reviewed and abstracted, and subjects were classified as AIDS (criteria of the Centers for Disease Control) or as non-AIDS HIV-positive, most of whom had constitutional symptoms, findings, or histories consistent with ARC. Table 1 summarizes patient characteristics.

Between 7 PM and 9 PM, each subject was placed in a supine position, and an indwelling catheter was placed in a superficial arm vein using a three-way connector through which normal saline was infused slowly. Baseline samples were taken approximately 30 minutes before and again immediately before administering the releasing factors. The four hypothalamic-releasing factors were prepared in individual syringes and then injected in rapid sequence over 1 to 2 minutes in the following order[30,31]: TSH-releasing hormone (TRH) 250 μg, gonadotropin-releasing hormone (GnRH) 100 μg, ovine ACTH-releasing hormone (oCRH) 80 μg, and human GH-releasing hormone(1-44 amide) (GHRH) 80 μg. These dosages and the sequence are similar to those used by Sheldon et al[30] and Cohen et al[31] in studies reporting the diagnostic validity of the four releasing factors used in rapid sequential fashion. Subsequent blood samples were taken at 30, 60, and 90 minutes after injecting the releasing factors. All subjects were monitored closely for reactions to the releasing factors. No significant changes in blood pressure or pulse were observed in any subject. However, transient facial flushing associated with a feeling of warmth was noted in 80% of all subjects, and transient nausea, palpitations, the urge to urinate, and a peculiar, unpleasant taste were described by some subjects.

A portion of each blood sample was collected in cold centrifuge tubes containing EDTA and protease inhibitor (Trasylol; Mobay Chemical, New York, NY). The tubes were quickly centrifuged, and plasma was removed and frozen for later measurement of ACTH levels by immunoassay. The remainder of each blood sample was allowed to clot on ice, and the serum was stored at −20°C until used for assay of all other hormones. For each hormone, all samples from each subject were analyzed in the same assay, and all assays were performed using commercial immunoassay kits and reagents. The cortisol kit was from Cambridge Medical Diagnostics (Billerica, MA), and the ACTH kit was from Radioassay Systems Laboratory (Carson, CA). Intraassay and interassay coefficients of variation were less than 10%. Serum TSH concentrations were measured using an immunoradiometric assay kit (Gammacoat; Baxter) modified to achieve even greater sensitivity (9 μU/L), defined as the concentration of TSH exceeding the zero standard by 2 SD. It had intrassay and interassay coefficients of variation of less than 8% at 0.5 and 20 mU/L. Serum fT_4 concentrations were measured using a commercial kit (Gammacoat; Baxter-Travenol, Cambridge, MA). Coefficients of variation within and between assays were less than 9% at fT_4 concentrations of 1 and 26 pmol/L. Serum LH and total testosterone concentrations were measured with kits from Diagnostic Products (Los Angeles, CA). Assay sensitivity for LH was less than 0.2 IU/L, and for total testosterone, less than 0.3 nmol/L. Intraassay and interassay coefficients of variation were 5% to 12% for both LH and testosterone at the serum concentrations found. PRL was assayed using a monoclonal antibody in an immunoradiometric method (Irma-count; Diagnostic Products). GH level was measured using a specific primary antibody purchased from Radioassay Systems Laboratory, and ^{125}I-labeled (hGH) plus goat antirabbit second antibody was from Cambridge Medical Diagnostics. For each assay, the detection limit was 0.1 μg/L and intraassay and interassay coefficients of variation were less than 8%.

Synthetic oCRH and synthetic hGHRH were purchased from Bachem (Torrence, CA). CRH was dissolved in 5% mannitol, distributed into individual vials after sterile filtration, lyophilized, and stored at −70°C. hGHRH was dissolved in 2.5% aqueous mannitol and sterile-filtered, distributed into individual dosage vials, and stored at −70°C after lyophilization. Random vials of each releasing hormone were tested and found to be sterile and nonpyrogenic. Use of hGHRH and oCRH was approved by the Food and Drug Administration. Commercially available TRH (Relefact; Ferring, Suffern, NJ) and GnRH (Factrel; Wyeth-Ayerst, Philadelphia, PA) were used.

Table 1. Experimental Subjects

Group	Mean Age, yr (range)	Mean Body Weight, kg (range)	Associated Conditions (no.)	Major Medications (no.)
Control (n = 9)	40 (29-55)	77 (64-96)	—	—
ARC (n = 13)*	38 (32-51)	69 (59-80)	Depression (5)	Azidothymidine (11)
			History of	
			Weight loss (6)	Acyclovir (4)
			Diarrhea (4)	
			Hepatitis B (2)	Pentamidine (inhaled) (7)
			Syphilis (4)	Tranquilizer/antidepressant (5)
			Herpes zoster (2)	Phenytoin (1)
			Decreased libido (2)	Ketoconazole (2)
			Eosinophilia (3)	
			Leukopenia (2)	
AIDS (n = 13)†	34 (22-52)	72.6 (57-89)	Depression (4)	Azidothymidine (12)
			History of	
			Weight loss (5)	Pentamidine (inhaled) (7)
			Pneumocystis (8)	Acyclovir (5)
			Hepatitis B (2)	
			Syphilis (2)	
			Atypical mycobacterium (4)	Tranquilizer/antidepressant (3)
			Kaposi's sarcoma (3)	
			Decreased libido (6)	Ketoconazole (2)
			Eosinophilia (6)	
			Leukopenia (7)	Insulin (1)

*Mean CD_4, 190; range, 25-479.

†Mean CD_4, 32; range, 11-88.

For each subject, the maximum increment of change for each hormone was calculated by subtracting the basal value (defined as the average of the −30-minute and zero-time values) from that subject's peak stimulated value. Results for each hormone were averaged by group (AIDS, ARC, and control) and compared using one-way ANOVA followed by Tukey's procedure with SAS (SAS Institute, Cary, NC) statistical programs. Controls were also compared with all HIV-positive subjects (AIDS and ARC) using a *t* test with Bonferroni correction. When normal distribution of data could not be verified, comparisons were made using log-transformed data or the Wilcoxon rank-sum test. Within groups, correlations were estimated using the Spearman rank correlation coefficient. Time courses of the responses were analyzed by repeated-measures ANOVA followed by univariant ANOVA if differences were detected.

No significant changes in serum fT_4 concentrations in response to TRH were found in any of the groups, and consequently, only basal values are shown in the figures and tables.

All subjects provided informed consent, and the project was approved by the Human Subjects Review Committee of the University of California, Davis.

RESULTS

Time courses of the mean serum responses of pituitary hormones and cortisol to the rapid sequential injection of the releasing factors are summarized in Fig 1. For GH and PRL, basal levels are within the normal range and there are no significant differences from the control group (Fig 1A and B). However, stimulated levels of both hormones are significantly greater ($P < .02$) in the AIDS group than in the controls at all times sampled after administration of the releasing factors. The same trend for PRL and GH is found in the ARC group following injection of the releasing factors, although statistical significance is reached in this group only for the stimulated GH concentrations.

The most striking features of the ACTH serum concentrations are the considerably higher baseline values in both HIV-infected groups ($P < .05$; Fig 1C). The ACTH response to oCRH was also greater in both infected groups than in controls. Generally, peak cortisol responses in ARC and AIDS groups were not different from responses in

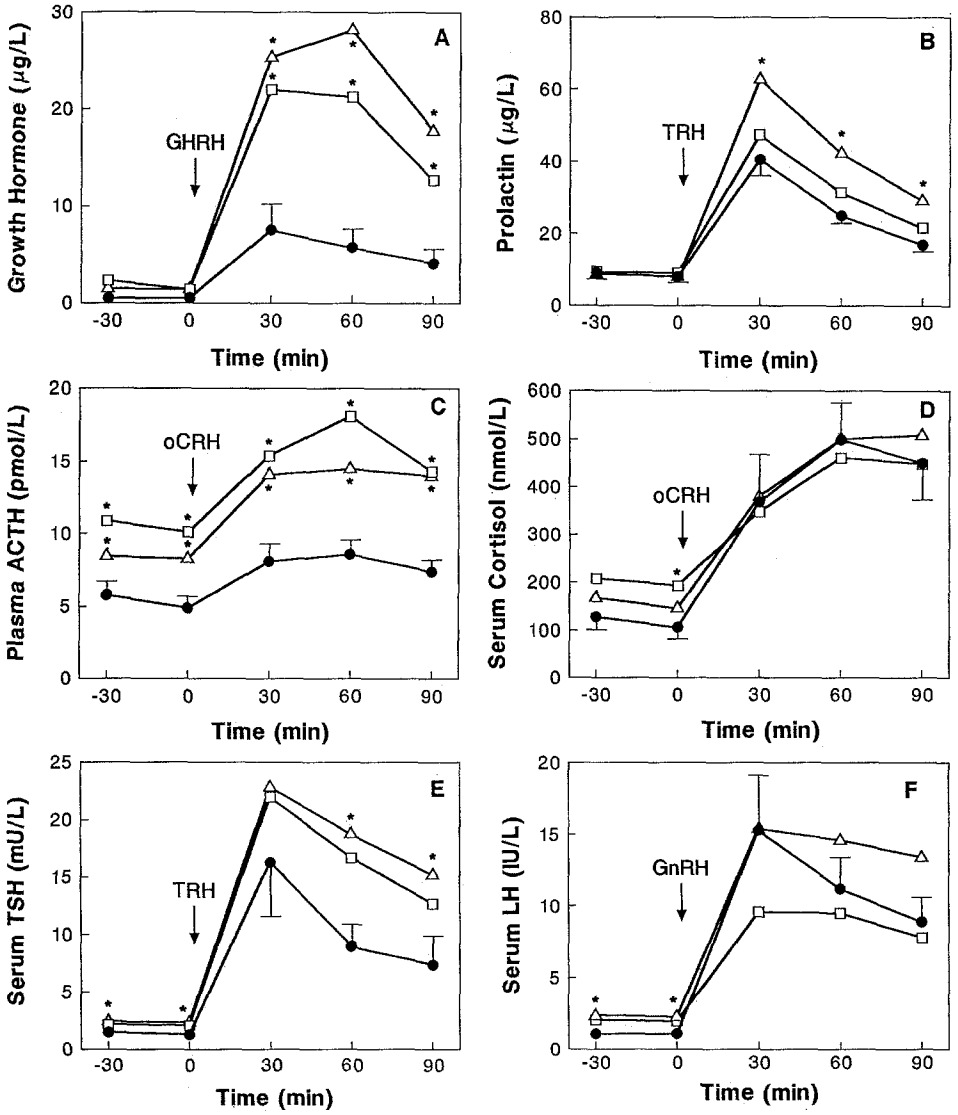

Fig 1. Time course of serum hormonal responses to releasing hormones. (●) Mean of the control group, with brackets indicating 1 SE; (△) mean of the AIDS groups; (□) mean of the non-AIDS HIV-infected group. ARC group SE brackets are omitted from AIDS and ARC groups for clarity. *Significantly different from control group mean ($P < .02$ for A and B; $P < .05$ for C to F).

controls, whereas basal cortisol levels were higher only in the ARC group (Fig 1D). Interestingly, the ARC group had baseline ACTH and cortisol levels even greater than the levels in the AIDS group.

At all time points, including basal values taken before TRH administration, mean TSH concentrations in HIV-infected groups were higher than in the control group (Fig 1E). This difference was statistically significant ($P < .05$) only for the AIDS group at baseline and at 60 and 90 minutes after TRH, and is accompanied by a significantly lower basal mean fT_4 level in the AIDS group (Table 2). It should be noted that all mean values for serum TSH and serum fT_4 concentrations are within the usual "normal" range.

Basal serum LH concentrations in both HIV-infected groups were greater than in controls, whereas peak responses were not different from controls, resulting in lower incremental responses in the ARC group and all HIV groups (Table 2).

Table 2 shows that although basal plasma ACTH levels were significantly greater in each of the HIV-infected groups, responses to oCRH (peak and incremental) were also increased. Baseline cortisol concentrations in the ARC group and all HIV-infected groups were increased significantly, consistent with elevated basal ACTH levels. However, cortisol responses were not increased following CRH administration despite exposure to significantly higher concentrations of ACTH. The previously noted greater mean GH response to GHRH in all HIV-infected groups is apparent ($P < .02$), as is the increased PRL response (to TRH) in AIDS subjects.

Table 2. Basal Serum Hormone Levels and Responses to Releasing Hormones

Hormone	Control (n = 9)	ARC (n = 13)	AIDS (n = 13)	All HIV (n = 26)
LH (IU/L)				
Basal	1.1 ± 0.1	2.08 ± 0.3*	2.4 ± 0.4*	2.18 ± 0.3*
Peak	15.3 ± 8.0	10.0 ± 1.6	16.4 ± 2.3	13.2 ± 1.5
Increment	14.2 ± 3.9	8.0 ± 1.5*	14.0 ± 2.0	11.0 ± 1.4*
Testosterone (nmol/L)				
Basal	18.0 ± 2.0	18.7 ± 2.4	18.7 ± 2.0	18.7 ± 1.4
Peak	22.0 ± 1.7	25.0 ± 2.8	24.3 ± 2.8	24.6 ± 1.7
Increment	4.9 ± 1.4	6.6 ± 1.4	5.6 ± 1.4	5.9 ± 1.0
TSH (mU/L)				
Basal	1.4 ± 0.3	2.1 ± 0.4	2.5 ± 0.4*	2.3 ± 0.3
Peak	16.6 ± 4.7	22.0 ± 4.0	23.6 ± 3.5	22.8 ± 2.6
Increment	14.9 ± 4.6	19.9 ± 3.7	21.1 ± 3.2	20.5 ± 2.4
fT_4 (pmol/L)				
Basal	20.6 ± 1.4	19.7 ± 1.4	17.1 ± 0.9*	18.4 ± 0.8
ACTH (pmol/L)				
Basal	5.3 ± 0.8	10.5 ± 1.8*	8.4 ± 0.8*	9.4 ± 1.0†
Peak	9.3 ± 1.0	19.1 ± 3.9*	15.6 ± 1.5*	17.3 ± 2.0†
Increment	4.0 ± 0.7	8.6 ± 3.2*	7.2 ± 1.1*	7.9 ± 1.6†
Cortisol (nmol/L)				
Basal	117 ± 26	210 ± 26*	156 ± 22	179 ± 16*
Peak	503 ± 25	408 ± 16	528 ± 36	505 ± 19
Increment	386 ± 25	279 ± 24*	372 ± 26	326 ± 19*
GH (μg/L)				
Basal	0.5 ± 0.1	1.9 ± 1.0	1.4 ± 0.4	1.6 ± 0.5
Peak	8.2 ± 2.6	24.3 ± 3.4†	30.5 ± 4.7†	26.5 ± 3.0†
Increment	7.7 ± 2.6	22.4 ± 3.6†	29.1 ± 4.8†	25.9 ± 3.0†
PRL (μg/L)				
Basal	8.4 ± 1.7	9.3 ± 1.2	8.3 ± 1.3	8.8 ± 0.9
Peak	40.6 ± 4.5	47.5 ± 7.1	63.1 ± 5.5†	55.3 ± 4.7
Increment	32.1 ± 5.0	38.3 ± 6.7	54.7 ± 5.2†	46.5 ± 4.5

NOTE. Results are expressed as the mean ± 1 SE.

*$P < .05$ *v* control.

†$P < .02$ *v* control.

Figure 2 shows serum hormone concentrations found in individual HIV-infected subjects relative to the group means (±1 SD) for control subjects. The distribution of stimulated GH concentrations in individual subjects with AIDS was similar to that in individuals with ARC (Fig 2A). Ten subjects (of 13) in each HIV-infected group had peak responses exceeding the control mean ±1 SD. PRL responses were similar but less marked, with seven AIDS subjects exceeding the mean control peak response by 1 SD or more (Fig 2B). A majority of subjects in both HIV-infected groups had basal serum LH concentrations greater than the control mean, yet only one subject (with AIDS) had a peak response greater than 1 SD over the control mean response (Fig 2C). The distribution of individual basal serum total testosterone concentrations in both groups of HIV-infected men is reasonably symmetrical about the control mean (Fig 2D). Examination of both LH and testosterone concentrations in individual subjects shows low testosterone concentrations (<7 nmol/L) in two subjects, both of whom had basal LH concentrations near the control mean and modest—not decreased or exaggerated—LH responses to GnRH. A single individual in the ARC group had high basal testosterone levels (>35 nmol/L) and a barely detectable basal serum LH concentration that did not respond to GnRH. He denied taking exogenous testosterone. Eight of 26 HIV-infected subjects complained of decreased libido and potency, but only one of these had a clearly low serum testosterone concentration (the AIDS subject with the lowest testosterone). The other four subjects with low testosterone levels (<12 nmol/L) had no complaints of impotence.

Figure 2E and F illustrates that a substantial portion of HIV-infected subjects in both groups (ARC and AIDS) had basal and stimulated plasma ACTH concentrations that were greater than the control means. A similar distribution of individual basal cortisol levels is apparent in both HIV-infected groups, but the pattern of peak stimulated cortisol concentrations is not significantly different in these groups as compared with the controls. Incremental serum cortisol responses were generally decreased in HIV-infected subjects having the highest basal cortisol concentrations ($P < .03$, Spearman rank correlation). Of interest is the single individual (ARC) with the smallest incremental cortisol response; he had the highest basal cortisol concentration and a negligible response (60 nmol/L, or ~2 μg/dL) to CRH, yet his basal and stimulated ACTH levels were near the means of the control group.

The distributions of individual serum TSH and fT_4

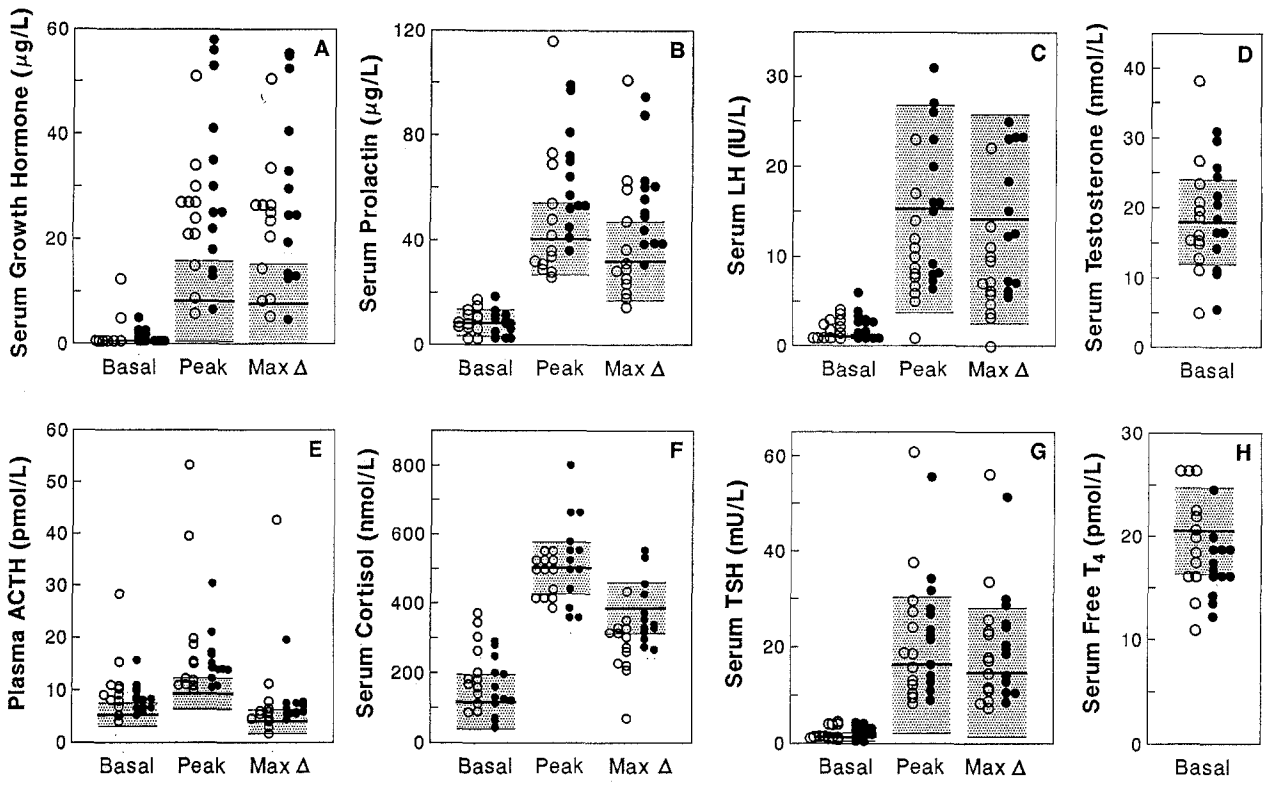

Fig 2. Distribution of individual serum hormone concentrations in HIV-infected subjects. Basal, peak stimulated, and maximal increments for each hormone are shown for each AIDS subject (●) and for each non-AIDS HIV-positive subject (○). (▨) Mean ± SD of nine control subjects.

concentrations are not quite symmetrical about the control means, with more individuals in both HIV-infected groups having decreased fT_4 levels and increased basal and stimulated TSH levels (Fig 2G and H). Of five subjects with the lowest T_4 concentrations, four had increased basal TSH levels and the highest stimulated TSH concentrations.

DISCUSSION

The majority of HIV-infected subjects in this study had a history of symptoms commonly observed in this condition, and most were on multiple medications, as summarized earlier. However, all were being evaluated as outpatients, and only one subject required hospitalization within 4 weeks of being studied. No correlation could be found between basal or stimulated levels of any hormone assayed and age, body weight, specific symptoms, or specific medications. However, the individual with the smallest cortisol response was taking ketoconazole, and another subject with low serum testosterone concentrations (and complaining of impotence) was also taking ketoconazole, yet neither had increased basal or stimulated levels of the appropriate pituitary trophic hormone.

Although HIV-infected men (both ARC and AIDS groups) had basal serum GH concentrations not significantly different from controls, they responded in an exaggerated fashion to hGHRH. Similarly, mean basal PRL concentrations in HIV-infected groups were similar to levels in the control group, whereas PRL responses to TRH tended to be greater in HIV-positive men, reaching statistical significance only in the group with AIDS. Published data regarding GH secretion in HIV-infected patients are limited.[26-28] There has been a case report of isolated GH deficiency in a child with perinatally acquired AIDS.[26] In a retrospective study of HIV-infected males with hemophilia, three were found to have growth retardation.[27] Although stimulated GH concentrations were normal in those three subjects, somatomedin C concentrations and mean 24-hour GH levels were decreased in two subjects, suggesting impaired neuroregulation of GH secretion. Another study[28] found only one child of nine with AIDS and failure to thrive had an impaired GH response to arginine, but the serum somatomedin C level was normal. Our data indicate that GH secretion in response to GHRH is increased in adult men with AIDS or ARC; serum somatomedin C concentrations were not measured. The basis for the increased pituitary GH response to GHRH is unclear. Control of GH secretion is complex and still incompletely understood,[32-38] and GH responses to GHRH in normal adults are extraordinarily variable,[30,32,39] presumably reflecting a lack of control of factors important in regulating responsiveness of somatotropes, somatostatin secretion, and/or the pulsatile pattern of GHRH secretion itself.[32] Our studies were all performed at the same time of day (early evening), and although the controls were somewhat older and heavier, GH response was not correlated with age or weight. The effect of age on GH response to GHRH is disputed, in any case. [38,39] Peak and incremental GH responses in our control group were lower, on average, than those reported

by Sheldon et al[30] or Cohen et al[31] using a similar protocol. The reason for this is unclear, although one difference is that all of our subjects were given the releasing factors in the early evening, not in the morning. Additionally, an inhibitory effect of CRH on GH responses to GHRH has been described[40] when both releasing hormones are given simultaneously, and TRH has been reported to stimulate GH release in patients with renal disease or acromegaly. Although such interactions of releasing factors were not found in normal subjects,[30,31] inhibiting/stimulatory effects could occur in HIV-infected subjects responding to the injection of multiple releasing factors. We did not study GH responses to individual releasing factors, nor was an attempt made to verify biological activity of the assayed immunoreactive GH.

PRL responses to TRH in the AIDS group were significantly increased, and were not correlated in control or HIV-positive subjects with basal TSH or PRL levels or with TSH responses to TRH. PRL responses in individual subjects were not correlated with medications used, symptoms of impotence, or LH/testosterone levels. Dobs et al[13] found normal basal PRL concentrations in HIV-positive subjects (most with AIDS) and normal stimulation with TRH in four subjects with hypogonadotropic hypogonadism. Elevated basal PRL concentrations were found in hypogonadal AIDS and ARC subjects by Croxson et al,[15] and Verges et al[19] reported basal "hypersecretion" of PRL in HIV-positive men regardless of severity of disease, as well as increased PRL response to TRH. Yet another study reported that asymptomatic HIV-infected men have normal basal PRL levels.[18] The basis for such conflicting results regarding basal and stimulated PRL concentrations is unknown, but direct involvement of the pituitary by HIV or by associated infections seems unlikely.[7,8] Possibly, the increased PRL response to TRH in AIDS subjects results from progression of central nervous system abnormalities found in HIV-infected subjects[41] or from consequences of lymphokines or other immunomodulators on the hypothalamic-pituitary axis.[42]

Statistically, AIDS and ARC subjects have significantly increased basal plasma ACTH concentrations in the evening. Peak and incremental ACTH responses to oCRH are also increased in these HIV-infected subjects as compared with healthy male controls. Basal evening cortisol levels are also higher in the HIV-infected groups, but peak responses are not different from those in the controls. Consequently, incremental responses of cortisol to oCRH in HIV-infected subjects are less than in controls—despite exposure to greater basal and peak ACTH concentrations. One of four subjects taking ketoconazole had elevated baseline and peak ACTH levels with entirely normal basal and stimulated cortisol concentrations; another subject had an increased basal cortisol level and the smallest cortisol response despite basal and stimulated ACTH levels similar to those in control subjects.

The finding of increased basal cortisol levels and decreased cortisol increments to oCRH stimulation may reflect inapparent "stress,"[43,44] with the decreased cortisol increment merely reflecting the increased basal level.[45,46] Yet there was a significant positive correlation between basal and stimulated (peak) levels of cortisol and between basal and peak ACTH levels in each group ($P \leq .05$, Spearman rank correlation). Previous studies of pituitary-adrenal function in HIV-infected subjects have yielded variable results, although all report puzzling abnormalities. Generally, basal cortisol levels have been found to be elevated,[12,14,17,19] although contrary results were found in asymptomatic HIV-infected subjects.[18] Cortisol responses to exogenous ACTH have been reported to be normal or decreased even though basal cortisol levels were elevated[12,19] or decreased.[18] Oberfield et al[14] found enhanced cortisol responses to exogenous ACTH. Data on ACTH concentrations are more limited. Villette et al[17] found decreased mean levels of ACTH over a 24-hour period—together with elevated cortisol levels—leading them to speculate that a non-ACTH factor was directly stimulating cortisol production. Verges et al[19] found elevated basal ACTH concentrations in non-AIDS HIV-infected subjects, but not in subjects with more advanced HIV infections. A recent study[47] of 25 HIV-infected patients without AIDS, including five females, showed that 50% had inadequate incremental responses of serum cortisol to oCRH. Of these, about half had little or no incremental ACTH response to CRH, indicating that the deficient cortisol response was due to impaired pituitary secretion of ACTH. Interestingly, the mean basal serum cortisol level in HIV-infected patients was increased. Other studies have found evidence of primary adrenal insufficiency[12,13,26,48] in 2% to 20% of symptomatic HIV-infected subjects. A study of hyponatremic AIDS patients reported that 14 subjects (of 48) had inappropriately increased plasma concentrations of arginine vasopressin, suggesting nonosmolar stimulation of vasopressin release,[49] which could augment ACTH release. The largest study of adrenocortical function in AIDS was reported by Membreno et al,[12] who examined basal and corticotropin-stimulated serum steroid levels in 74 hospitalized patients with AIDS and 19 with ARC. Basal serum cortisol levels were increased and cortisol responses to acute ACTH stimulation were subnormal. Four AIDS patients had adrenal insufficiency without elevated plasma ACTH concentrations, indicating abnormal hypothalamic-pituitary function. Our results are most consistent with those reported by Membreno et al,[12] Verges et al,[19] and Azar and Melby.[47] Basal cortisol levels are increased but incremental cortisol responses to oCRH are decreased despite higher basal, peak, and incremental concentrations of immunodetectable ACTH. These results suggest that ACTH secretion is "activated" in our HIV-infected subjects, and although baseline cortisol production is similarly stimulated, the adrenal is unable to respond fully to further ACTH increases caused by exogenous oCRH. The basis for the activated ACTH secretion observed in the HIV-infected subjects is unclear. In addition to increased endogenous CRH possibly related to stress,[43,44] it is speculated that other hypothalamic factors (eg, arginine vasopressin) and immunomodulating substances (eg, lymphokines) may be involved.[12,17,42,49,50] It is also possible that the increased ACTH concentrations found reflect immunoreactive forms

having decreased biological activity. The basis for the decreased incremental cortisol response observed in HIV-infected subjects is also obscure, but based on our results, it is not caused by an insufficient ACTH response to CRH. Evidently, adrenocortical responsiveness to ACTH is impaired in HIV-infected subjects,[12,19] conceivably due to direct effects of HIV or related processes (eg, cytomegalovirus, immunomodulators, or antiadrenal antibodies) on the adrenal or to a decrease in the bioactivity of the secreted ACTH.

Although complaints of decreased libido and decreased potency are common in HIV-infected men, the basis for such complaints is obscure. Dobs et al[13] found that 50% of men with AIDS were hypogonadal, with decreased serum total testosterone concentrations (relative to normal or asymptomatic HIV-infected men) but normal LH levels. Yet seven (of eight tested) had normal LH responses to GnRH. Similar but less marked decreases in total serum testosterone concentrations were reported by Croxson et al,[15] but LH levels were significantly increased, suggesting primary Leydig cell insufficiency. However, all of those tested had adequate testosterone responses to hCG, indicating appropriately responsive Leydig cells. Similarly, Villette et al[17] found a modest decrease in mean plasma total testosterone concentrations in six AIDS subjects (but not in seven asymptomatic men infected with HIV). However, elevated total serum testosterone levels and elevated free testosterone concentrations have been reported in 39 asymptomatic HIV-infected subjects.[18] In that study, although basal LH levels were not different from levels in healthy controls, the response of LH (but not FSH) to GnRH was also increased in HIV-infected men. These results were interpreted as indicating altered hypothalamic-pituitary function of unknown cause.[18] A study of 51 HIV-seropositive men ranging from CDC class II (asymptomatic) to CDC class IV found that total serum testosterone concentrations were slightly decreased only in class IV subjects, whereas all classes of HIV-positive men had significantly increased basal and GnRH-stimulated serum concentrations of both LH and FSH.[19] These results are consistent with primary Leydig cell insufficiency occurring early in HIV infection. Results reported here for 13 men with AIDS and 13 HIV-infected men without AIDS are different still from the results summarized earlier. No significant differences in mean serum total testosterone concentrations were found between control and HIV-infected groups. Although baseline LH levels and LH responses to GnRH were also within normal ranges, basal LH values were significantly greater in both HIV-infected groups than in healthy controls. But maximal (peak) LH responses to GnRH did not differ significantly from those of controls. Although serum free testosterone concentrations and serum levels of sex hormone–binding globulin were not measured in the current study, other reports have indicated that sex hormone–binding globulin levels are normal in HIV-infected men and that concentrations of free testosterone parallel those of total testosterone.[13,15,18] Our results suggest a modest defect in Leydig cell function requiring a somewhat increased LH concentration to maintain normal testosterone concentration, in agreement with Croxson et al[15] and Verges et al.[19] However, the normal or decreased—not exaggerated—LH response to GnRH suggests that pituitary LH secretion is also impaired.[51,52] Convincing evidence for hypogonadism was found in only two of our subjects, one each in the AIDS and ARC groups, although four others had borderline-low testosterone levels. Only one of these had complaints of impotence, and he was the only one of these six on ketoconazole; yet his baseline LH was only 3 IU/L, and it responded modestly to GnRH (peak, 9.2 IU/L). Consequently, primary hypogonadism alone—whether the result of ketoconazole or other HIV-related processes—does not explain the LH values. There is considerable evidence that systemic illness, acute illness, acute burns, starvation, aging, and a variety of medications can decrease serum testosterone concentrations.[53-57] LH and testosterone results in our subjects could not be correlated with weight loss, use of specific medications (including ketoconazole), serum PRL levels, or even symptoms of decreased libido and impotence.

Clinically significant thyroid dysfunction is evidently uncommon in AIDS subjects[13,20-22] and is not a significant contributor to the weight loss frequently observed.[23] Studies have reported findings partly consistent with acute systemic illness, including decreased serum total triiodothyronine concentrations that correlated with mortality.[20-22] In subjects with the most advanced disease (class IV), fT_4 concentrations have also been found to be decreased,[23,24] but serum T_4-binding globulin concentrations are reported to be increased in AIDS subjects.[20,22] However, modest increases in basal serum TSH concentrations have been described for AIDS subjects,[19,24] as well as exaggerated TSH responses to TRH. Coupled with the high prevalence of antithyroid antibody reported in AIDS subjects,[24] these results are consistent with subclinical primary hypothyroidism. Our results of significantly greater baseline and stimulated TSH concentrations in AIDS subjects, together with modestly decreased basal fT_4 levels in the same subjects, also indicate the presence of a modest subclinical primary impairment of thyroid function in this group.

From our studies, it appears that there is a general—but not uniform—increase in immunoassayable hormonal secretion by the anterior pituitary in basal and/or stimulated states in patients infected with HIV. The basis for these changes (increased basal levels of TSH, LH, ACTH, and cortisol, and increased stimulated levels of GH, PRL, TSH, and ACTH) is unknown. Possible factors include the presence of stress and progressive illness, concurrent changes in target organs related to HIV or associated infections, and immune or infectious changes in the central nervous system together with the effects of cytokines and other immunomodulators. We speculate that the increased pituitary activity observed is due to modestly impaired target organ function and to increased hypothalamic stimulation of the pituitary.

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