The Hypothalamic-Pituitary-Adrenal Axis in Critical Illness: Response to Dexamethasone and Corticotropin-Releasing Hormone

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ABSTRACT

Plasma ACTH and cortisol concentrations are frequently elevated in patients in intensive care units (ICU). To examine the functional integrity of the hypothalamic-pituitary-adrenal axis during critical illness, we evaluated prospectively 53 ICU patients in a general medical ICU. Thirty-one patients and 7 normal controls underwent an overnight dexamethasone suppression test (3 mg dexamethasone, orally, at 2300 h). Plasma ACTH and serum cortisol were measured at 0900 h. In a separate experiment, 22 patients and 7 control subjects underwent a CRH stimulation test [100 μg human (h) CRH, iv]. ACTH and cortisol concentrations were determined from −15 to 120 min. Compared to normal controls, plasma ACTH and serum cortisol concentrations were not fully suppressible by dexamethasone [mean ± SEM: plasma ACTH, 21 ± 4 $vs.$ 3 ± 0.5 pg/mL (4.7 ± 0.9 $vs.$ 0.7 ± 0.1 pmol/L); serum cortisol, 13.9 ± 1.9 $vs.$ 1.5 ± 0.3 μg/dL (390 ± 50 $vs.$ 40 ± 10 nmol/L); P = 0.0001], demonstrating an altered glucocorticoid feedback in the ICU patients. Patients undergoing hCRH stimulation had clearly elevated mean baseline plasma ACTH and serum cortisol concentrations [ACTH, 78 ± 20 pg/mL $vs.$ 15 ± 3 in controls (17.2 ± 4.4 $vs.$ 3.4 ± 0.7 pmol/L; P = 0.007); cortisol, 36.8 ± 3.4 μg/dL $vs.$ 9.6 ± 1.2 (1020 ± 80 $vs.$ 260 ± 30 nmol/L; P = 0.0001)]. Despite elevated baseline glucocorticoid concentrations, stimulation with hCRH resulted in significantly higher peak plasma ACTH concentrations 15 min after hCRH than in controls [134 ± 31 $vs.$ 48 ± 9 pg/mL (29.5 ± 6.8 $vs.$ 10.6 ± 2.0 pmol/L); P < 0.05]. Serum cortisol concentrations in ICU patients were significantly elevated throughout the test period (P = 0.0001) and rose to a peak of 43.9 ± 3.5 μg/dL compared to 18.2 ± 2.0 μg/dL in controls (1210 ± 70 $vs.$ 500 ± 60 nmol/L). We conclude that ICU patients have a markedly altered responsiveness of their pituitary corticotroph to suppression with dexamethasone and stimulation with hCRH. These findings may be explained by altered pituitary glucocorticoid feedback and/or hypersecretion of peptides with CRH-like activity (vasopressin and cytokines) during critical illness. (J $Clin$ $Endocrinol$ $Metab$ **77**: 151–156, 1993)

PREVIOUS studies demonstrated that critical illness, such as in patients in intensive care units (ICU), is associated with changes in the hypothalamic-pituitary-adrenal (HPA) (1–10), hypothalamic-pituitary-thyroid (11–13), and gonadal (14–18) axes; the renin-angiotensin system (19–22); and the sympathoadreno-medullary system (6, 23). The response of the HPA axis has been shown to be essential for adaptation and maintenance of homeostasis during critical illness (24). One of the main functions of glucocorticoids seems to be modulation and coordination of the stress response by interacting with other elements of the stress defense (*i.e.* hormones, cytokines, lipid mediators of inflammation, and bioactive peptides) (24).

Patients in ICUs have elevated baseline cortisol concentrations, which are positively correlated with the degree of illness as well as with the mortality rate (5, 7). Furthermore, patients in ICUs have, compared to controls, higher cortisol levels after stimulation with ACTH-(1–24), reflecting adaptation of the adrenal cortex during major stress (5, 10). The baseline adrenal steroid secretion shows a shift away from adrenal androgen and mineralocorticoid secretion toward glucocorticoid secretion (1, 15, 17, 19, 20).

The regulation of the HPA axis during critical illness has not been studied in detail. We, therefore, studied the response of the HPA axis to suppression with dexamethasone and stimulation with human (h) CRH in 53 ICU patients and 14 normal controls.

Subjects and Methods

Patients

The study was performed during a 6-month period in the medical ICU of the Medical Department II, Krankenhaus Merheim, University of Koln. Krankenhaus Merheim is an 800-bed tertiary care hospital. The ICU is a 9-bed unit, treating approximately 400 patients/yr, mainly patients with cardiac or renal disease. The frequency of respirator treatment is 50%. The protocol was approved by the Institutional Review Board, University of Koln, and all patients or their first degree relatives and all normal subjects gave written informed consent.

Patients were enrolled in this study regardless of the medical condition responsible for transfer to the ICU. They were studied as soon as informed consent could be obtained and as soon as their medical condition had been stabilized. Routine medical treatment was given as required. Patients with known diseases of the HPA axis, hypoxic brain damage, glucocorticoid treatment, gastrointestinal bleeding, fever higher than 38.5 C, or emergency procedures, such as surgery, within 48 h were excluded from the study.

In all 53 patients studied, age, sex, main diagnosis, and outcome (inhospital mortality) were determined. The severity of illness was assessed on the day the tests were performed using the Therapeutical Intervention System Score (TISS-24) (25), which estimates the degree of illness by

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measuring the intensity of treatment given to a particular patient. Blood was drawn from either peripheral indwelling catheters or internal jugular venous catheters.

Dexamethasone suppression test

Thirty-one patients and seven normal subjects underwent an overnight dexamethasone suppression test. Clinical data for the study population are shown in Table 1. At 0900 h on day 1, blood was drawn for determination of plasma ACTH and serum cortisol. At 2300 h, all subjects received 3 mg dexamethasone, orally (nonintubated patients) or via a gastric tube (patients receiving respirator therapy), followed by determination of plasma ACTH and serum cortisol the following day at 0900 h.

hCRH stimulation test

In a separate experiment, 22 patients and 7 normal subjects underwent a hCRH test at 0900 h in the morning. The characteristics of the

TABLE 1. Clinical profile of patients who had a dexamethasone suppression test

	Controls	ICU patients
n	7	31
Sex	5F/2M	15F/16M
Age (yr)	58 ± 14	67 ± 11
Day of test after admission to ICU		6.1 ± 3.9 (2–16)[a]
Mean TISS		32 ± 10
Respiratory therapy (%)		39
Mortality (%)		41
Main diagnosis		
Myocardial infarction		7
Chronic heart failure		5
Cardiogenic shock		6
Acute renal failure		4
Chronic renal failure		5
Liver failure		2
ARDS		2

F, Female; M, male; TISS, Therapeutical Intervention System Score; ARDS, adult respiratory distress syndrome.

The mean ± SD are shown.

[a] Range is in parentheses.

TABLE 2. Clinical profile of patients who had a hCRH stimulation test

	Controls	ICU patients
n	7	22
Sex	5F/2M	6F/16M
Age (yr)	61 ± 11	64 ± 12
Day of test after admission to ICU		6.0 ± 6.15 (2–25)[a]
Mean TISS		39 ± 10 (15–54)
Respiratory therapy (%)		82
Mortality (%)		68
Main diagnosis		
Myocardial infarction		2
Chronic heart failure		3
Pulmonary edema		2
Cardiogenic shock		4
Acute renal failure		2
ARDS		2
Liver failure		4
Sepsis/septic shock		3

F, Female; M, male; TISS, Therapeutical Intervention System Score; ARDS, adult respiratory distress syndrome. Shown are the mean ± SD.

[a] Range is in parentheses.

subjects are shown in Table 2. After 2 baseline blood samples for determination of plasma ACTH and serum cortisol (−15 and 0 min), hCRH (Corticobiss, Bissendorf Peptide, Hannover, Germany) was injected as a bolus dose of 100 μg, iv. Blood was drawn at 15, 30, 45, 60, 90, and 120 min.

Hormone assays

Plasma ACTH was determined after extraction with Quso G_{32} (Philadelphia Quartz Co.) (26). The lower limit of detection was 3 pg/mL. Serum cortisol was measured by a commercial enzyme-linked immunosorbent assay (Serozym, Serono, Freiburg, Germany). The inter- and intraassay coefficients of variation were below 9% and 6% for both assays, respectively. All samples from a patient were measured in the same assay.

Data analysis

The total and net integrated ACTH and cortisol responses to hCRH were calculated by the trapezoid method and expressed as the area under the concentration-time curve (AUC) from 0–120 min. All values are expressed as the mean ± SEM, if not otherwise stated. Statistical significance of the differences was assessed using the Mann-Whitney U test for unpaired data. Correlations were examined with linear regression analysis and expressed as the Pearson's correlation coefficient. $P \leq 0.05$ was considered statistically significant.

Results

Dexamethasone suppression test

Compared to normal subjects, baseline plasma ACTH concentrations at 0900 h were slightly, but not significantly, higher in ICU patients, whereas baseline cortisol concentrations were clearly elevated (Fig. 1). After dexamethasone
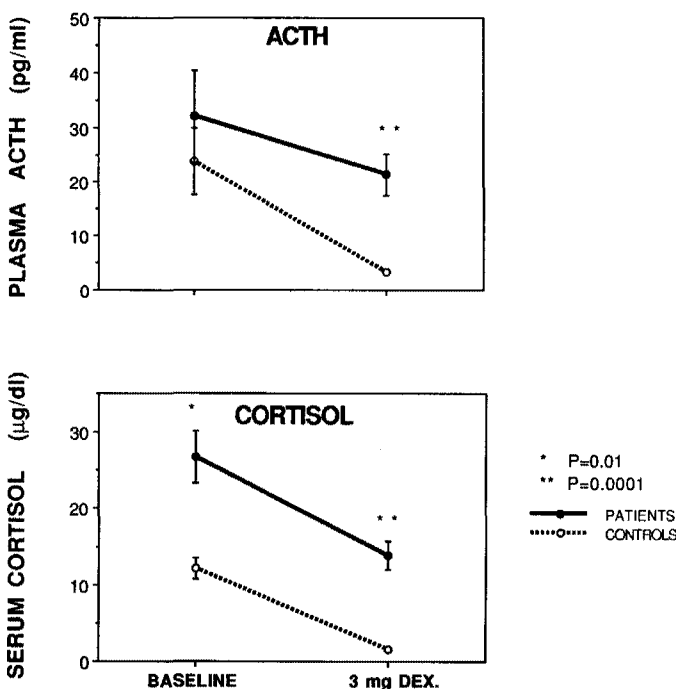

FIG. 1. Mean responses of plasma ACTH and serum cortisol to suppression with dexamethasone in 7 normal controls and 31 ICU patients. To convert ACTH concentrations to picomoles per L, multiply by 0.2202; to convert cortisol concentrations to nanomoles per L, multiply by 27.6.

administration, plasma ACTH as well as cortisol concentrations were suppressed in normal subjects. In contrast, ICU patients showed significantly elevated mean ACTH ($P = 0.0001$) and cortisol concentrations ($P = 0.0001$), demonstrating an altered negative feedback regulation of glucocorticoids during critical illness.

ACTH and cortisol concentrations in ICU patients were significantly correlated with the in-hospital mortality rate (Table 3). Patients who later died during the hospital stay had higher postdexamethasone ACTH concentrations ($P = 0.02$) and cortisol concentrations ($P = 0.04$) than patients who were discharged from the hospital.

hCRH stimulation test

Baseline plasma ACTH concentrations showed a great variability in ICU patients, but were significantly higher than those in the controls (Fig. 2; $P = 0.007$). In addition, baseline cortisol concentrations were significantly elevated ($P = 0.0001$). The individual ACTH response to hCRH in ICU patients was characterized by an ACTH increase ranging from 7–450% of the baseline value and was not dependent on the baseline cortisol concentrations ($r = 0.05$; $P = 0.8$). Mean ACTH concentrations rose to a peak of 134 ± 31 pg/mL (29.5 ± 6.9 pmol/L) 15 min after the injection of hCRH compared with 48 ± 9 pg/mL (10.6 ± 2.0 pmol/L) in control subjects ($P = 0.046$; Fig. 2). The total AUC and the maximum ACTH concentrations (Fig. 3), but not the net AUC, were also significantly higher than those in controls.

Mean cortisol concentrations in ICU patients were significantly elevated throughout the test period ($P < 0.0001$), and the total AUC for cortisol was clearly higher than that in controls ($P = 0.0001$). The cortisol increase in ICU patients ($P = 0.8$) as well as the net AUC ($P = 0.4$) were similar in ICU patients and controls.

Baseline ACTH concentrations were significantly higher in patients who later died during the hospital stay than those in patients who survived and were discharged from the hospital [95 ± 28 vs. 42 ± 16 pg/mL (20.9 ± 6.1 vs. 9.2 ± 3.5 pmol/L); $P = 0.04$]. In addition, the total AUC of nonsurvivors was significantly higher than that in control subjects ($P = 0.04$; Table 3), whereas survivors did not have significantly higher total AUC than controls. Baseline serum cortisol concentrations and the total time-integrated cortisol

secretion did not differ between patients who later died and patients who survived.

Discussion

The response of the HPA axis has been shown to be an integral part of the adaptation to emotional and physical stress. Critical illness, such as in ICU patients, is one of the most powerful activators of the HPA axis. ACTH and cortisol concentrations in sepsis (8), after extensive burns (15) or brain trauma (9), or in shock are elevated and may reach extraordinarily high levels depending on the degree of illness. Whereas it is well established that ICU patients have biochemical evidence of hypercortisolism, little is known of the functional integrity of the HPA axis during critical illness. The data from our dynamic evaluation show that the response of the HPA axis to suppression by dexamethasone and stimulation by hCRH is profoundly altered in ICU patients. Treatment of ICU patients with dexamethasone at a dose that easily suppresses ACTH and cortisol secretion in normal subjects was minimally effective in our patients. In addition, stimulation with hCRH resulted in an augmented ACTH response in spite of very high baseline cortisol concentrations, which probably would have been sufficient to blunt or abolish the hCRH-induced ACTH surge in normal subjects. Taken together, the observed abnormalities in the HPA axis of ICU patients are unique and have not been reported in any of the well characterized biochemically hypercortisolemic states, such as major depression (27), pregnancy (28), and renal insufficiency (29). The comparison to the findings in major depression is particularly noteworthy, since chronic emotional stress associated with depression may be seen as a counterpart to the chronic physical stress of ICU patients. Similar to ICU patients, patients with depression are also hypercortisolemic and show a blunted cortisol response to suppression with dexamethasone (27). However, the response to exogenous stimulation with CRH in depressed patients is characterized by a blunted ACTH response, presumably because of the negative feedback of elevated endogenous glucocorticoids on ACTH release. In contrast, in ICU patients, the negative feedback of endogenous glucocorticoids on pituitary ACTH secretion is clearly altered, and stimulation with hCRH results in high plasma ACTH concentrations in spite of elevated baseline cortisol

TABLE 3. Influence of subsequent mortality on ACTH and cortisol responses to dexamethasone and CRH

|	Dexamethasone suppression test				hCRH stimulation test	
	Basal ACTH [pg/mL (pmol/L)]	ACTH after 3 mg dex [pg/mL (pmol/L)]	Basal cortisol [μg/dL (nmol/L)]	Cortisol after 3 mg dex [μg/dL (nmol/L)]	Total AUC ACTH (pg/mL· min)	Total AUC cortisol (μg/ dL·min)
Controls	24 ± 6 (5.3 ± 1.2)	3 ± 0.5 (0.7 ± 0.1)	12.1 ± 1.2 (330 ± 30)	1.5 ± 0.3 (40 ± 10)	4,390 ± 570	1,881 ± 213
Patients						
Survivors	26 ± 10 (5.7 ± 2.2)	18 ± 5 (3.9 ± 1.1)[a]	19.5 ± 1.9 (330 ± 50)[a]	11.4 ± 2.3 (310 ± 60)[a]	6.740 ± 2,110	4,586 ± 455[a]
Nonsurvivors	41 ± 15 (9.0 ± 3.3)	28 ± 7 (6.2 ± 1.5)[a,b]	37.0 ± 6.9 (1020 ± 220)[a,c]	17.3 ± 2.9 (480 ± 80)[a,c]	14,470 ± 3,980[c]	5,166 ± 567[a]

[a] $P < 0.02$ vs. controls.
[b] $P < 0.02$ vs. survivors.
[c] $P < 0.05$ vs. survivors.
[d] $P < 0.05$ vs. controls.

FIG. 2. Mean responses of plasma ACTH and serum cortisol to stimulation with hCRH in 7 normal controls (CON., CO.) and 22 ICU patients (PAT., PA.). The *insets* show the total (TOT) and net integrated (NET) hormone responses, expressed as the secretory AUC. To convert ACTH concentrations to picomoles per L, multiply by 0.2202; to convert cortisol concentrations to nanomoles per L, multiply by 27.6.
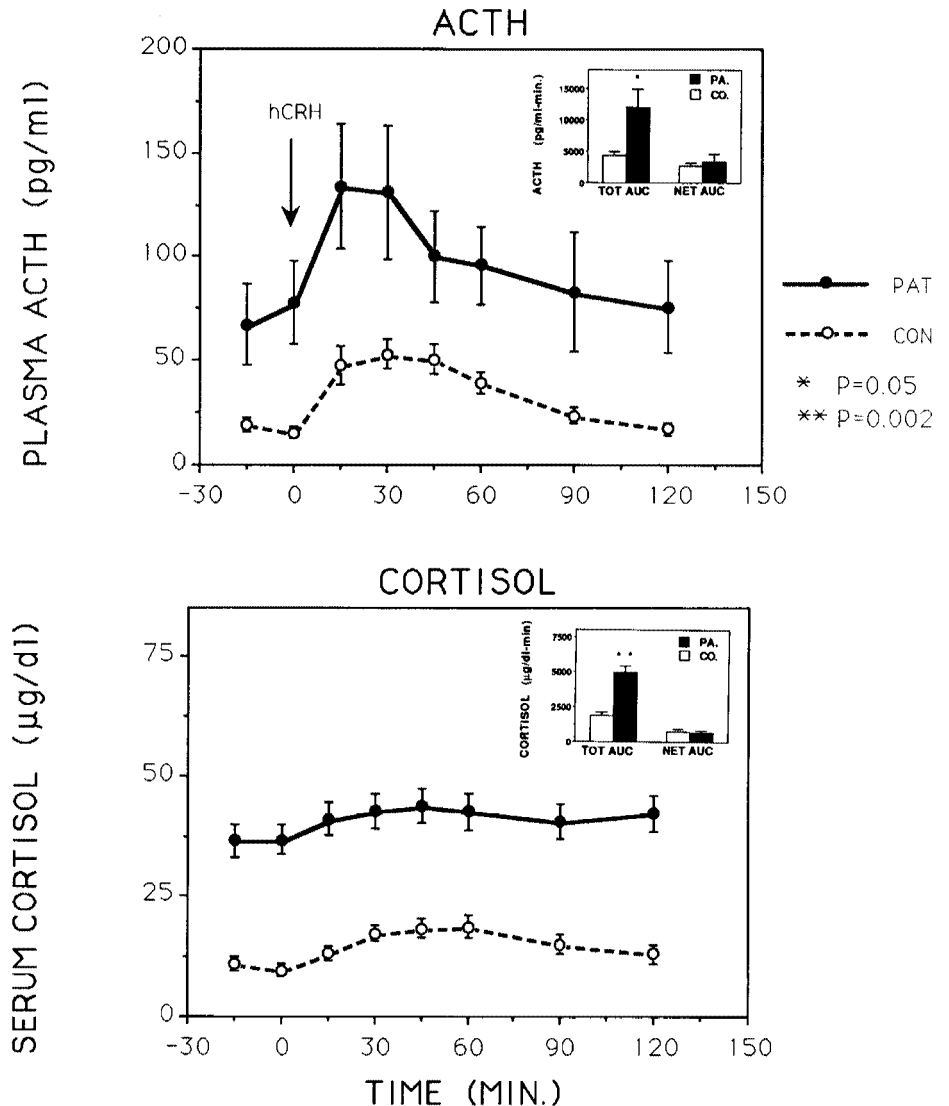
levels. This observation may be explained in several ways.

The responsiveness of the pituitary corticotroph to exogenous CRH in the presence of high endogenous glucocorticoid levels may be due to diminished sensitivity of the corticotroph to glucocorticoids in critically ill patients. Pituitary resistance to glucocorticoids in ICU patients could be caused by abnormalities in the transduction of the effects of glucocorticoids. Recently, a subgroup of acquired immunodeficiency syndrome patients was identified who had cortisol resistance characterized by elevated ACTH and cortisol concentrations and a diminished glucocorticoid receptor affinity in circulating mononuclear cells (30). Similar alterations in glucocorticoid receptor function may be partially responsible for changes in the HPA axis of ICU patients and could result in an augmented ACTH response to CRH.

Alternatively, the ACTH hypersecretion in ICU patients may also be explained by elevated levels of peptides and hormones with CRH-releasing properties, which exaggerate the effects of endogenous and exogenous CRH on pituitary ACTH release. Vasopressin is a stress hormone frequently elevated during major surgery and severe illness (31). It exhibits a synergistic effect on ACTH release when given in combination with CRH (32–34). Its action makes it a likely candidate for the observed activation of the HPA axis during critical illness. Other peptides involved in CRH and ACTH release which may be elevated during major stress include angiotensin-II (35) and neuropeptide-Y (36).

Another explanation for activation of the HPA axis during critical illness is the interaction between the immune and neuroendocrine systems. The inflammatory cytokines interleukin-1β, interleukin-6, and tumor necrosis factor-α are frequently elevated in ICU patients (37, 38) and have prognostic significance. Endotoxin administration to normal volunteers is associated with a probably cytokine-mediated ACTH and cortisol release (39). In addition, interleukin-1β, interleukin-6, and tumor necrosis factor-α have CRH- and/or ACTH-releasing properties *in vivo* and *in vitro* (40–45). These potent peptides may, therefore, stimulate ACTH and cortisol secretion in critical illness.

Critical illness is often associated with conditions such as
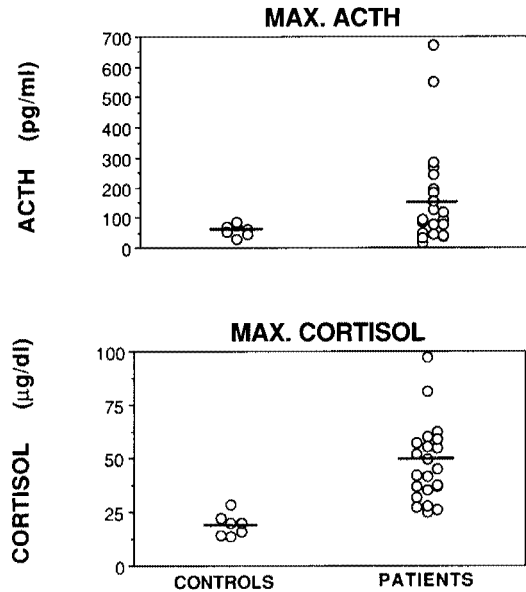
MAX. ACTH

MAX. CORTISOL

FIG. 3. Maximum plasma ACTH and serum cortisol concentrations after stimulation with hCRH in 7 normal controls and 22 ICU patients. The mean ACTH ($P = 0.05$) and cortisol concentrations ($P = 0.0002$) were significantly different in the 2 groups. To convert ACTH concentrations to picomoles per L, multiply by 0.2202; to convert cortisol concentrations to nanomoles per L, multiply by 27.6.

liver failure and acute renal insufficiency, which may affect the half-lives of plasma ACTH and cortisol in ICU patients. Although there are no data available concerning cleavage and metabolic clearance of ACTH and cortisol, respectively, in these patients, these conditions alone could theoretically result in elevated plasma ACTH and cortisol concentrations due to altered metabolism of these hormones. However, the plasma ACTH and cortisol responses to stimulation with hCRH in ICU patients and normal controls were parallel, arguing against a significantly prolonged half-life of these hormones.

In conclusion, ICU patients have a markedly altered responsiveness of their pituitary corticotroph to suppression with dexamethasone and stimulation with hCRH during critical illness. These findings are most likely due to hypersecretion of peptides with CRH-like activity during life-threatening illness. However, pituitary resistance to glucocorticoids as a result of alterations in the signal transduction pathway of glucocorticoids cannot be excluded.

Acknowledgments

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