

ORIGINAL ARTICLES

Stress hormones in accident patients studied before admission to hospital

Wolfgang Hetz, Hans D Kamp, Ulrich Zimmermann, Andreas von Bohlen, Ludwig Wildt, Juergen Schuettler

Abstract

Objective—To assess stress hormone response in traumatised patients studied at the site of injury and on their way to hospital.

Methods—The study was prospective. Blood samples were taken from 77 patients immediately after the arrival of the emergency physician at the site of the accident (t_1) and shortly before patients' admission to hospital (t_2). Plasma concentrations of β endorphin, cortisol, adrenocorticotrophic hormone (ACTH), prolactin, and growth hormone were measured.

Results—Trauma in out-of-hospital patients resulted in remarkably increased concentration of growth hormone within minutes. ACTH, cortisol, and prolactin were only moderately increased.

No significant correlations were found between hormone levels and blood pressure or heart rate. The plasma ACTH concentration was significantly lower before admission to hospital than immediately after the accident. Plasma cortisol, prolactin, and growth hormone concentrations were not significantly different between the two points of observation. In samples taken immediately after the accident (t_1), there was a positive correlation between both β endorphin and prolactin and the injury severity score, whereas cortisol levels were negatively correlated with injury severity score, suggesting impaired cortisol release from the adrenal cortex after severe injury. At t_1 , ACTH was correlated with cortisol and β endorphin. Patients with head injuries had hormone concentrations similar to those without head injuries but with a similar injury severity score from injuries in other parts of the body.

Conclusions—Lower cortisol concentrations in the very severely injured might be due to failure of the adrenal cortex to respond normally to ACTH stimulation. Growth hormone seems to play a major role in the response to trauma, reflecting an immediate stress response.

(J Accid Emerg Med 1996;13:243-247)

The plasma concentrations of adrenocorticotrophic hormone (ACTH), cortisol, β endorphin, prolactin, and growth hormone have not been studied in injured humans immediately after an accident but before admission to hospital. Activation of the hypothalamic-pituitary-adrenal axis is elicited by major trauma, such as long bone fracture, multiple injury, burns, and head injury.¹⁻⁶ There are, however, as yet no reports concerning the magnitude and time course of stress hormone secretion during the immediate post-traumatic phase, and in-hospital drug treatment and haemodilution by volume infusions may alter the concentrations of hormones.

To avoid this problem, we took blood samples for determination of these hormones before emergency treatment at the accident site. Another objective was to determine whether there was a correlation between hormone concentrations and the severity of injury. Finally, we investigated the effect of head injury on the anterior pituitary hormone response to trauma by comparing this response in traumatised patients with or without head injury.

Methods

The study was prospective and was conducted in trauma patients treated on-scene by the helicopter rescue team, SAR Nuremberg 74.

The study group consisted of 77 consecutively treated adults (59 male, 18 female) who had suffered injuries, including head injuries, caused by accidents. Accident site data acquisition was performed by an emergency physician of the department of anaesthesiology of Erlangen University Hospital. Emergency treatment was started immediately after the team arrived at the site of accident. This included establishment of an intravenous line which was used to take the first blood sample before administration of fluids or drugs. Further treatment was performed at the site of accident according to common trauma management rules. If necessary, patients received opiates. Patient demographics, site and severity of the injury, heart rate, and blood pressure were documented. All patients were taken to hospital by the rescue helicopter. Shortly before admission to hospital a second blood sample was taken. Samples were taken between 7 am and 10 pm. All samples were taken in summer. The interval between the first and second

Department of Anaesthesiology, University Hospital, Erlangen, Germany
W Hetz

Department of Anaesthesiology, Central Hospital, Bremen, Germany
H D Kamp

Department of Psychiatry, University Hospital, Erlangen, Germany
U Zimmermann

Department of Anaesthesiology, Martha Maria Hospital, Nuremberg, Germany
A von Bohlen

Department of Gynaecology, University Hospital, Erlangen, Germany
L Wildt

Department of Anaesthesiology, University Hospital, Erlangen, Germany
J Schuettler

Correspondence to: Wolfgang Hetz MD, Department of Anaesthesiology, University Hospital, Maximiliansplatz, 91054 Erlangen, Germany

Accepted for publication 20 December 1995

Key terms: trauma; β endorphin; stress hormones

Table 1 Demographic data of patients and time intervals. Values are medians (range)

Characteristic	Data
Age (years)	34 (14-68)
Injury severity score	17 (4-75)
Interval from accident to first blood sample (min)	23 (5-81)
Interval from first to second blood sample (min)	35 (15-91)

samples was determined by the duration of flight. During flight no samples could be taken. The median interval between accident and obtaining the first blood sample was 23 minutes (table 1). An injury severity score (ISS) was allocated by scoring injuries to the various body regions, as described by Baker *et al.*⁷

The study was approved by the local ethics committee of the University of Erlangen.

Each of the 10 ml blood samples was collected in a prechilled plastic syringe, then immediately put into a chilled test tube containing liquid ethylenediaminetetra-acetic (EDTA) (Monovette) and placed on ice until centrifugation at 3000 rpm for 10 min. The plasma was then separated and stored at -70°C until analysis. All these steps were performed within 1 h on board the helicopter by a medical student brought as an additional crew member.

Plasma β endorphin concentrations were estimated by radioimmunoassay (RIA) kit (Incstar), with a sensitivity of 3.9 pmol/litre. According to usual RIA data processing procedures, sensitivity was defined by a difference from B (0) of three times its standard deviation. β Lipotrophin was not specifically extracted, since cross reactivity between β endorphin and β lipotrophin was less than 5%, on a molar basis.

ACTH was measured by RIA (Incstar) with a sensitivity of 3.8 pmol/litre. The normal range in our laboratory is less than 17 pmol/litre. Plasma cortisol and growth hormone measurement was by RIA (Diagnostic Products Corp) with a sensitivity of 0.01 $\mu\text{mol/litre}$ and 0.9 ng/ml, respectively. The normal cortisol range in our laboratory is 0.28-0.56 $\mu\text{mol/litre}$. The normal growth hormone range lies below 1 ng/ml.

Plasma prolactin was determined using an IRMA (immune-radiometric assay; Serono Diagnostics) with a sensitivity of 0.3 ng/ml. The normal range is less than 20 ng/ml.

The control ranges referred to morning blood samples.

STATISTICAL ANALYSIS

Because the assumption of approximately normal distribution was not satisfied, the Wilcoxon signed rank test was used to evaluate differences in the plasma measurements between two times of measurement.

For investigation of correlation between pairs of variables, the distribution-free rank correlation coefficient of Spearman (ρ) was used. Statistical significance was considered to be at the $P < 0.05$ level.

Results

The mean injury severity score of the patients was 17. Twenty eight of them had head injuries.

The plasma ACTH concentration was higher immediately after the accident than before admission to hospital. The difference was highly significant ($P < 0.001$) (table 2).

Median plasma cortisol, prolactin, and growth hormone concentrations were not significantly different between the two points of observation (table 2). Compared with normal values, the growth hormone and prolactin concentrations were markedly increased.

A significant difference was found between the median β endorphin concentrations on arrival and at t_2 (table 2).

No significant correlation could be detected between concentrations of any of the hormones and arterial blood pressure or heart rate at t_1 or t_2 .

A positive correlation was found between arrival β endorphin and injury severity score ($\rho = 0.360$, $P < 0.01$) (fig 1). The correlation was still significant before admission to hospital ($\rho = 0.354$, $P < 0.05$).

There was also a correlation between prolactin concentrations and injury severity score on arrival (t_1) ($\rho = 0.331$, $P < 0.01$) (fig 2), whereas at t_2 the correlation was not significant.

A weak but significant negative correlation was seen between plasma cortisol concentrations and severity of trauma on arrival ($\rho = -0.254$, $P < 0.05$) (fig 3). At the second observation point before admission to hospital the correlation failed to reach statistical significance.

At neither measurement point was a significant correlation found between ACTH or growth hormone concentrations and injury severity score.

When blood samples were taken immediately after the accident, there was a correlation between plasma ACTH and plasma cortisol concentrations ($\rho = 0.343$, $P < 0.01$). At t_2 the correlation was not significant. Significant positive correlations were found at t_1 between β endorphin and both ACTH and prolactin (table 3).

Hormone concentrations were studied separately in patients whose injuries were predominantly of the head ($n = 19$). These patients were compared with patients whose injuries were entirely outside the head region (49 patients). There was no significant difference in the injury severity score values of the two groups. There was no difference in plasma hormone concentrations between patients with predominant head injuries and those without head injuries.

Discussion

This is the first study to investigate plasma concentrations of β endorphin, ACTH, cortisol, prolactin, and growth hormone in injured humans immediately after an accident and before admission to hospital. The accidents occurred at various times of day. According to a study by Barton *et al.*,⁸ the time of day at which samples were taken has no effect on initial plasma cortisol concentrations. Barton concluded that in injured patients

Table 2 Plasma hormone concentrations of first (t_1) and second (t_2) blood sample and level of statistical significance for the comparison between t_1 and t_2 . Values are medians (range)

Hormones	t_1	t_2	P
β Endorphin (pmol/litre)	26.17 (0-140)	23.8 (0-104.4)	<0.01
Cortisol (μ mol/litre)	0.65 (0.02-1.38)	0.60 (0.08-1.59)	NS
Adrenocorticotrophin (pmol/litre)	21.5 (4.3-90.6)	15.2 (4.9-61.3)	<0.001
Prolactin (ng/ml)	24.5 (1.9-105.4)	28.4 (6.8-121.0)	NS
Male	23.5 (1.9-65.5)	25.9 (6.8-52.3)	NS
Female	61.1 (16.2-105.4)	59.1 (17.6-121.0)	NS
Growth hormone (ng/ml)	5.95 (0.5-44.4)	6.9 (0.9-35.7)	NS

The normal range of values is given after the name of the hormone in the left column.

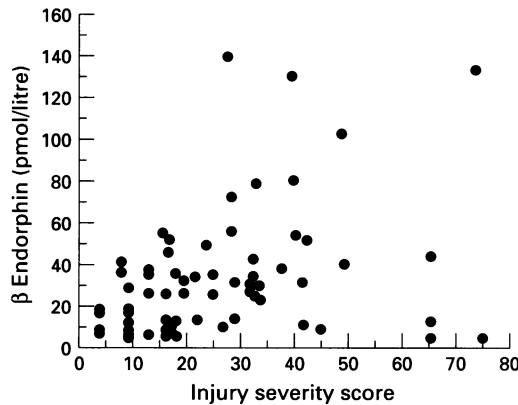


Figure 1 Correlation between initial plasma β endorphin concentrations (t_1) and injury severity score. (Spearman rank correlation coefficient = 0.36; $P < 0.01$.)

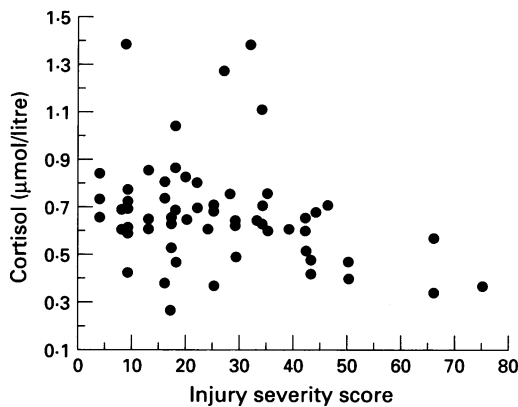


Figure 2 Correlation between initial plasma prolactin concentrations (t_1) and injury severity score. (Spearman rank correlation coefficient = 0.331; $P < 0.01$.)

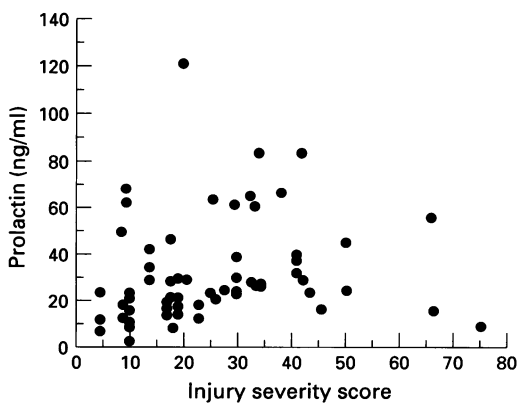


Figure 3 Correlation between initial plasma cortisol concentrations (t_1) and injury severity score. (Spearman rank correlation coefficient = -0.254; $P < 0.05$.)

standardisation of the time of sampling is not necessary at an early stage.

Previous studies have disagreed over the magnitude of the rise in ACTH concentration and its relation to injury severity in patients studied in hospital. During cardiopulmonary resuscitation ACTH concentrations were found to be markedly raised.⁹ Several studies on ACTH immunoreactivity have been done after burns.^{10 11} Combining the data taken over the first five days, Brizio-Molteni *et al*¹⁰ found a generally negative relation with the area of burn. In all patients taken together, ACTH on "day 1 am" was similar to control values; it thereafter tended to rise and then fall below control levels. Vaughan *et al*¹¹ described high cortisol levels with ACTH levels not correspondingly elevated after severe burns. Barton *et al*,⁸ in contrast, found plasma ACTH concentrations after accidental injury to be markedly increased compared to the normal range. In patients with minor and moderate injuries (ISS 1-12) ACTH was correlated with injury severity score when samples were taken within two hours of injury but not when taken later; in more severely injured patients there was no correlation with injury severity score.⁸ Our findings show only a moderate increase in plasma ACTH and no relation with injury severity score in injured patients before admission to hospital.

In our study plasma cortisol concentrations were only moderately increased (fig 3). Unexpectedly low plasma cortisol concentrations have also been observed by others in patients with major trauma.^{12 13}

We found a weak, but significant negative relation between cortisol and injury severity score over the whole ISS. The results contrast with those from a previous study which showed a biphasic relation between plasma cortisol concentration and injury severity score,⁸ moderately injured patients having plasma cortisol concentrations in proportion to the severity of their trauma, while those with more severe injuries (ISS 25-50) had lower concentrations. However, patients in that study were not as severely injured as in our investigation.

We could show a weak but significant correlation between ACTH and cortisol concentrations when blood samples were taken immediately after the accident. Significance was absent at later times. Barton *et al*⁹ found plasma cortisol to be positively correlated with plasma ACTH, but the relation was statistically significant only in patients with injury severity scores of 13-24. A poor correlation between ACTH and cortisol may be due to the pulsatile release of ACTH in irregular bursts.¹⁴⁻¹⁷ Although in normal subjects the peaks of ACTH are generally accompanied by increases in plasma cortisol and within subjects the two hormones are generally positively correlated,^{15 16} this correlation does not always extend to single samples taken from different individuals.¹⁸ Sequential measurements of plasma cortisol after major surgery suggested that in surgical trauma stimulation of the adrenal cortex was

Table 3 Correlations between plasma hormone concentrations of first (t_1) and second (t_2) blood samples

Hormones	t_1		t_2	
	ρ	P	ρ	P
ACTH-cortisol	0.343	0.007	0.294	NS
ACTH- β endorphin	0.388	0.002	0.313	NS
β endorphin-prolactin	0.332	0.009	0.251	NS

ρ = Spearman rank correlation coefficient.

also episodic.¹⁹ However, episodic secretion cannot completely explain the poor correlation between cortisol and ACTH concentrations. Unexpectedly, though plasma cortisol fell in relation to injury severity score, ACTH did not. A possible explanation for lower cortisol concentrations in the very severely injured might be failure of the adrenal cortex to respond normally to ACTH stimulation because of decreased adrenal blood flow secondary to shock. A general decrease in stress response seems not to have occurred, because other stress hormones such as growth hormone were markedly increased. Woolf *et al.*,⁶ however, described a significant positive relation between circulating cortisol concentrations and the magnitude of neurological dysfunction in patients with brain injury. They emphasise that it is unclear whether the raised cortisol concentrations contribute to the poor outcome or simply reflect the severity of injury. This finding was not due simply to non-specific stress, because cortisol levels predicted patient outcome weeks to months later.

There are very few studies describing β endorphin concentrations after trauma. The only recent study that succeeded in relating β endorphin to injury severity score was that of Lloyd *et al.*,²⁰ investigating serum β endorphin concentrations in injured children. These patients, however, were only moderately injured. In contrast to our results, Lloyd found no consistent effect of time interval from injury to blood sampling on the detected β endorphin values. Zimmerman *et al.*²¹ and Lopez²² found no relation between post-traumatic levels of serum β endorphin and the degree of neurological injury after severe head trauma.

The observed positive correlation between ACTH and β endorphin seems to be attributable to the fact that both hormones are derived from the common precursor (pro-opiomelanocortin - POMC). In the pituitary gland, β endorphin is synthesised as part of this much larger precursor hormone which contains sequences for ACTH and β lipotrophin, which is partially degraded to β endorphin.

As there is a relation between ACTH and β endorphin and the β endorphin concentrations are nearly always higher, we can conclude that after trauma β lipotrophin is mainly processed to β endorphin. Co-release of β endorphin and ACTH is well documented in normal subjects.²³⁻²⁶

In our investigation growth hormone, currently considered to be a long term stress hormone,²⁷ showed concentrations increased sixfold over reported normal values shortly

after the accident. Nevertheless, growth hormone concentrations did not show any relation to severity of injury. Chiolero *et al.*²⁸ studied growth hormone and prolactin in patients with severe trauma after hospital admission. They could not show any relation between severity of injury, as represented by injury severity score, and any of the measured hormone levels. Prolactin was increased in a patient group suffering from multiple injury combined with severe head injury, but was normal in the other groups. However, patients with raised prolactin had the highest injury severity scores, which is consistent with our finding of a positive correlation between prolactin and injury severity score. In the study of Chiolero *et al.*²⁸ growth hormone was increased in all groups. By contrast, patients suffering from severe craniocerebral trauma who were studied within 24 hours of the trauma showed no increase in plasma growth hormone concentrations at all.²⁹ From the present work we can conclude that, in contrast to a recent review of published reports,²⁷ growth hormone release seems to play a major role in the immediate response to trauma.

The finding of a positive correlation between β endorphin and prolactin raises the question of whether this is a causal interrelation or a simultaneous reaction to a common regulatory mechanism. The recent observation of raised prolactin levels after administration of β endorphin to healthy females³⁰ supports the first possibility. Also, central opioids are known to stimulate hypophyseal prolactin secretion by blocking the tonic dopaminergic inhibition.³¹ Our observation is therefore consistent with a central action of pituitary derived β endorphin, the possibility of which is currently under discussion.

There was no difference in plasma hormone concentrations between patients whose injuries were predominantly of the head injuries and those with other types of injury. These findings are in agreement with the results reported by Barton *et al.*⁹ and Lloyd *et al.*²⁰ By contrast, Chiolero *et al.*²⁸ found lower plasma concentrations of growth hormone and prolactin in patients with head injury than in patients without. Hackl *et al.*³² found normal plasma growth hormone concentrations in patients during the acute phase after severe craniocerebral trauma. King *et al.*³³ and Matsuura *et al.*,³⁴ however, reported an increase in growth hormone and prolactin soon after head injury of variable severity.

These results show a wide range of patterns of pituitary responses to head injury, but several factors may explain the discrepancies: (1) the severity of head injury, in particular the duration of coma, was not always comparable; (2) the time of measurement varied between hours after admission to hospital and five weeks after trauma; our study is the first to evaluate hormone concentrations before patients' hospital admission; (3) the pulsatile release of the pituitary hormones complicates interpretation of single plasma values, especially in view of the fact that most of patient groups in recent studies consisted of a

few patients only, whereas in our study 77 patients were investigated.

We know that cortisol and catecholamines act synergistically to augment vascular tone and myocardial contractility. Adrenal insufficiency in patients who are acutely ill has been defined as the inability to increase cortisol secretion in response to ACTH stimulation. The efficacy of physiological corticosteroid supplementation in improving haemodynamic stability and outcome during out-of-hospital trauma management in severely injured patients has yet to be studied.

- 1 Elliot M, Alberti KGMM. The hormonal and metabolic response to surgery and trauma. In: Kleinberger G, Deutsch E, eds. *New aspects of clinical nutrition*. Basel: Karger, 1983:245-70.
- 2 Evans EL, Butterfield WYH. The stress response in the severely burned. *Ann Surg* 1951;134:588-613.
- 3 King LR, McLaurin PL, Lewis HP. Plasma cortisol levels after head injury. *Ann Surg* 1970;172:975-84.
- 4 Moore FD. Endocrine changes after anesthesia, surgery, and unanesthetized trauma in man. *Recent Prog Horm Res* 1957;13:511-76.
- 5 Harris MJ, Baker RT, McRoberts JW, Mohler JL. The adrenal response to trauma, operation and Cosyntropin stimulation. *Surg Gynecol Obstet* 1990;170:513-6.
- 6 Woolf PD, Cox C, Kelly M, Nichols D, McDonald IV, Hamill RW. The adrenocortical response to brain injury: correlation with the severity of neurologic dysfunction, effects of intoxication, and patient outcome. *Alcohol Clin Exp Res* 1990;14:917-21.
- 7 Baker SP, O'Neill B, Haddon W, Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma* 1974;14:187-96.
- 8 Barton RN, Stoner HB, Watson SM. Relationships among plasma cortisol, adrenocorticotrophin, and severity of injury in recently injured patients. *J Trauma* 1987;27:384-92.
- 9 Lindner KH, Strohmenger HU, Ensinger H, Hetzel WD, Ahnefeld FW, Georgieff M. Stress hormone response during and after cardiopulmonary resuscitation. *Anesthesiology* 1992;77:662-8.
- 10 Brizio-Molteni L, Molteni A, Warpeha RL. Prolactin, corticotropin, and gonadotropin concentrations following thermal injury in adults. *J Trauma* 1984;24:1-7.
- 11 Vaughan GM, Becker RA, Allen IP. Cortisol and corticotrophin in burn patients. *J Trauma* 1982;22:263-72.
- 12 Carey LC, Cloutier CT, Lowery BD. Growth hormone and adrenal cortical response to shock and trauma in the human. *Ann Surg* 1971;174:451-8.
- 13 Meguid MM, Brennan MF, Aoki TT. Hormone-substrate inter-relationships following trauma. *Arch Surg* 1974;109:776-83.
- 14 Berson SA, Yalow RS. Radioimmunoassay of ACTH in plasma. *J Clin Invest* 1968;47:2725-51.
- 15 Krieger DT, Allen W. Relationship of bioassayable and immunoassayable plasma ACTH and cortisol concentrations in normal subjects and in patients with Cushing's disease. *J Clin Endocrinol Metab* 1975;40:675-87.
- 16 Tanaka K, Nicholson WE, Orth DN. Diurnal rhythm and disappearance half-time of endogenous plasma immunoreactive-MSH (LPH) and ACTH in man. *J Clin Endocrinol Metab* 1978;46:883-90.
- 17 Carnes M, Goodman BM, Lent SJ, Vo H. High intensity venous sampling reveals subtle alterations in plasma adrenocorticotropin patterns in old rats. *Endocrinology* 1993;133:608-15.
- 18 Daly IR, Fleisher MR, Chambers DJ. Application of the cytochemical bioassay for Corticotrophin to clinical and physiological studies in man. *Clin Endocrinol* 1974;3:335-45.
- 19 Wise L, Margraf HW, Ballinger WF. A new concept on the pre- and postoperative regulation of cortisol secretion. *Surgery* 1972;72:290-8.
- 20 Lloyd DA, Teich S, Rowe MI. Serum endorphin levels in injured children. *Surg Gynecol Obstet* 1991;172:449-52.
- 21 Zimmerman RS, Hayes RL, Morris DL, Lyeth BG, Dewey WL, Young HF. β -Endorphin in cerebrospinal fluid and serum after severe head injury. *Neurosurgery* 1990;26:764-70.
- 22 Lopez JA. Lack of correlation between β -endorphin and severity of cranial trauma [letter]. *Neurosurgery* 1991;28:335.
- 23 Guillemin R, Vargo T, Rossier J, Minick S, Ling N, Rivier C, et al. β -Endorphin and adrenocorticotropin are secreted concomitantly by the pituitary gland. *Science* 1977;197:1367-9.
- 24 Nakao K, Nakai Y, Jingami H, Oki S, Fukata J, Imura H. Substantial rise of plasma β -endorphin levels after insulin-induced hypoglycemia in human subjects. *J Clin Endocrinol Metab* 1979;49:838-41.
- 25 Nakao K, Nakai Y, Oki S, Horii K, Imura H. Presence of immunoreactive β -endorphin in normal human plasma. *J Clin Invest* 1978;62:1395-8.
- 26 Nakao K, Nakai Y, Oki S, Matsubara T, Koniski T, Imura H. Immunoreactive β -endorphin in human cerebrospinal fluid. *J Clin Endocrinol Metab* 1980;50:230-3.
- 27 Baue AE. Neuroendocrine response to severe trauma and sepsis. In: Faist E, ed. *The immune consequences of trauma, shock and sepsis*. Berlin: Springer, 1989:127-34.
- 28 Chiolero R, Lemarchand T, Schutz Y, De Tribolet N, Felber IP, Freeman I, et al. Plasma pituitary hormone levels in severe trauma with or without head injury. *J Trauma* 1988;28:1368-74.
- 29 Gottardis M, Nigitsch C, Schmutzhard E, Neumann M, Putensen C, Hackl JM, et al. The secretion of human growth hormone stimulated by human growth hormone releasing factor following severe cranio-cerebral trauma. *Intensive Care Med* 1990;16:163-6.
- 30 Reid RJ, Hoff ID, Yen SSC, Li CH. Effects of exogenous β -endorphin on pituitary hormone secretion and its disappearance rate in normal human subjects. *J Clin Endocrinol Metab* 1981;52:1179-84.
- 31 Carter D, Lightman SL. Opiates. In: Lightman SL, Everitt B, eds. *Neuroendocrinology*. Oxford: Blackwell, 1986:103-53.
- 32 Hackl JM, Gottardis M, Wieser C, Rimpl E, Stadler C, Schwarz S, et al. Endocrine abnormalities in severe traumatic brain injury - a cue to prognosis in severe craniocerebral trauma? *Intensive Care Med* 1991;17:25-9.
- 33 King LR, Knowles HC, McLaurin RL. Pituitary hormone response in head injury. *Neurosurgery* 1981;9:229-35.
- 34 Matsuura H, Nakazawa S, Wakabayashi I. Thyrotropin-releasing hormone-provocative release of prolactin and thyrotropin in acute head injury. *Neurosurgery* 1985;16:791-5.