Pattern of Activation of the Hypothalamic-Pituitary-Adrenal Axis in Acute Stroke
Relation to Acute Confusional State, Extent of Brain Damage, and Clinical Outcome

Klaus Fassbender, MD; Roland Schmidt, MD; Rainald Möhner, MD; Michael Daffertshofer, MD; Michael Hennerici, MD

Background and Purpose The aim of this study was to characterize the response of the hypothalamic-pituitary-adrenal system in the first hours of ischemic stroke and to relate its extent to the occurrence of acute confusional state, volume of brain damage, and clinical outcome.

Methods The secretion of corticotropin (adrenocorticotropic hormone [ACTH]) and cortisol was studied in 23 patients by determinations at hours 4, 6, 8, 10, and 14 and days 1, 3, 5, and 7 after onset of symptoms. Acute confusional state (DSM-III-R criteria), extent of lesion (volumetry of computed tomographic scans), and neurological and functional outcome (Scandinavian Stroke Scale, Barthel Index scores) were assessed.

Results The massive neuroendocrine response observed consisted of an initial phase with concomitantly increased levels of ACTH and cortisol and a second phase with decreased levels of ACTH while high concentrations of cortisol persisted. Initial levels of ACTH but not cortisol were significantly increased in patients with acute confusional state and significantly correlated with volume of brain lesion and neurological and functional outcome.

Conclusions An early and persisting activation of the hypothalamic-pituitary-adrenal axis was observed in relation to severity of disease. Its characteristic biphasic pattern suggests an initial central stimulation of release of ACTH followed by feedback suppression concomitant with an increased susceptibility of the adrenal gland. Because these hormones are known to exacerbate hypoxic injury to neurons, their massive release in hyperacute stroke may increase the extent of brain damage.

Key Words • hypothalamic-pituitary-adrenal axis • cerebral ischemia • confusion

Infection, trauma, or mental stress results in an increase in levels of cortisol. Increased concentrations of cortisol and a failure of the normal suppression of cortisol levels by dexamethasone have also been observed in acute stroke.

A number of studies have demonstrated the neurotoxicity of cortisol, suggesting that strong activation of the hypothalamic-pituitary-adrenal (HPA) axis may be an aggravating factor in acute cerebral ischemia. Increased plasma and urinary cortisol levels after stroke have been found to be associated with a high mortality rate and poor functional outcome.

Moreover, hypocortisolism in reaction to various types of stress has recently been related to acute confusional state, which is a common symptom in acute stroke, and hypercortisolism has been reported mainly in disoriented stroke patients.

However, the response of the HPA system in the important hyperacute phase of ischemic stroke has not yet been characterized. In this study the levels of these rapidly secreted and metabolized hormones are closely monitored in acute stroke beginning 4 hours after onset of symptoms; they are related to the occurrence of acute confusional state, volume of brain damage, and outcome of disease.

Subjects and Methods

In this study 23 patients (12 women, 11 men) aged 39 to 89 years (median, 72 years) were included within 4 hours after onset of the first symptoms of acute ischemic stroke. Nineteen patients had stroke in the carotid and 4 in the vertebrobasilar arterial territory. The diagnostic subgroups were large-vessel occlusive disease (n=5), cardiogenic disease (n=8), lacunar disease (n=4), and other or unknown (n=6). History, clinical examinations, computed tomographic (CT) scans, chest roentgenograms, electrocardiography, extensive laboratory workup, and daily follow-up were performed for diagnosis and to exclude patients with other causes of activation of the HPA axis (eg, those with surgical procedures within the last 3 weeks or those with concomitant preexisting or nosocomial infections). Patients receiving immunosuppressive agents, all types of steroids, and psychotropic drugs were excluded. One patient died at day 5. Standard therapy consisted of intravenous heparin (n=12) and low-dose subcutaneous heparin (n=11). The neurological and functional deficits were determined at day 1 and between the second or third week, according to standard criteria (Scandinavian Stroke Scale and Barthel Index). Acute confusional state (ACS) based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders,
ed 3, revised (DSM-III-R) for delirium was diagnosed from history, initial examination, and observation during the first days of hospitalization.

Determination of Volume and Location of Brain Damage
Computed tomographic scans were obtained at admission to show preexisting lesions and between days 3 and 14 to demonstrate the final lesion due to the present disease. The size of the brain lesion was quantified by two neurologists (R.M. and M.D.), who were blinded with regard to the clinical and neuroendocrinological data. The lesion area of the CT slices was manually determined; regarding slice thickness, the lesion volume was calculated using a computer-assisted planimetry algorithm. The measurements included all actual lesions but excluded older lesions. Additionally, the location of cerebral infarcts was determined.

Hormone Analyses
Venous blood samples for quantification of corticotropin (adrenocorticotropic hormone [ACTH]) and cortisol were collected from a venous catheter in precooled ethylenediaminetetraacetic acid (EDTA) tubes at hours 4, 6, 8, 10, and 14 and at days 1, 3, 5, and 7 (at 8 AM), centrifuged (5 minutes, 4°C, 3000 rpm), and stored at −80°C until used. All samples from an individual patient were measured in duplicate in a single assay to eliminate interassay variations. The LUMITest ACTH (Henning) is an immunoluminometric two-step assay for the determination of intact human ACTH in EDTA/plasma. Two monoclonal antibodies, one luminescent-labeled and the other immobilized on the inner surface of the tube, recognize different binding sites on ACTH to form a sandwich-type complex bound to the tube. The luminescence signal is directly proportional to the ACTH concentration. The normal range of ACTH is 10 to 60 pg/mL for 8 to 10 AM and 6 to 30 pg/mL for 8 to 10 PM. The limit of detection is 0.6 pg/mL. The measured intra-assay and interassay coefficients of variation were 4.8% and 9.8%, respectively. In the EnzymunTest Cortisol (Boehringer), serum cortisol and cortisol-peroxidase conjugate compete in the first incubation step for a limited quantity of specific antibodies coated onto the tube walls. The amount of antibody-cortisol-peroxidase complex, detected by the formation of a colored complex, is a measure of the cortisol content of the sample. The normal range is 250 to 700 nmol/L for 8 to 9 AM and 100 to 250 nmol/L for 8 to 10 PM. The detection limit was 30 nmol/L. The intra-assay and interassay coefficients of variation were less than 8% and 12%, respectively.

Statistical Analysis
Results are expressed as mean±SEM. For statistical analysis, the Wilcoxon matched-rank test, the Mann-Whitney U test, and Spearman’s rank correlation were used.

Results
Pattern of Release of ACTH and Cortisol
Concentrations of ACTH levels at hours 4 and 6 were significantly increased compared with levels at day 3 (P<.005 and P<.0005, respectively), day 5 (P<.01 and P<.005, respectively), and day 7 (P<.05 and P<.001, respectively) (Fig 1). Levels of cortisol also showed a strong increase, which, however, remained persistently elevated until day 5 (Fig 1). Compared with those at day 7, concentrations were significantly increased at hour 4 (P<.05), hour 6 (P<.005), hour 8 (P<.05), hour 10 (P<.005), hour 14 (P<.01), day 1 (P<.001), and day 3 (P<.01). Concentrations of hormones did not differ at any time in regard to sex and did not significantly correlate with age (data not shown).

Acute Confusional State
Nine of the 23 patients studied (39%) exhibited ACS. These patients showed significantly increased levels of ACTH at hour 4 (102.63±37.37 pg/mL) compared with those without this mental disorder (38.11±10.23 pg/mL, P<.05). Furthermore, the maximal ACTH levels of patients with (125.23±35.35 pg/mL) and without (52.74±8.33 pg/mL) ACS significantly differed (P<.05). In contrast, neither cortisol levels at any time studied nor maximal cortisol levels differed significantly in either group.

Neurological and Functional Deficits at Admission and Follow-up (Outcome)
At hour 4, but not later, concentrations of both ACTH and cortisol correlated significantly with the scores of the initial neurological examination (Scandi-
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navian Stroke Scale) \(r = -0.77\), \(P<0.05\) and \(r = -0.91\), \(P<0.005\), respectively). Similarly, maximal concentrations of ACTH and cortisol of each patient were significantly correlated with scores of the initial neurological examination \(r = -0.81\), \(P<0.05\) and \(r = -0.75\), \(P<0.05\), respectively). In contrast to those of cortisol, levels of ACTH significantly correlated with functional scores (Barthel Index) at admission \(r = -0.74\), \(P<0.05\), and only concentrations of ACTH at hour 4 correlated with neurological \(r = -0.71\), \(P<0.05\) and functional \(r = -0.74\), \(P<0.05\) outcome. Maximal concentrations of ACTH but not of cortisol were correlated with initial Barthel Index scores \(r = -0.75\), \(P<0.05\) as well as with neurological \(r = -0.81\), \(P<0.05\) and functional \(r = -0.74\), \(P<0.05\) outcome.

**Relation to Extent and Location of Brain Damage**

Levels of ACTH at hour 4 and the patients' maximal ACTH levels correlated significantly with the volume of brain lesion \(r = 0.67\), \(P<0.05\) and \(r = 0.60\), \(P<0.05\), respectively). There was a significant difference of levels of ACTH in patients with lesions \(>2\) cm\(^3\) \(n=13\) compared with those with lesions \(<2\) cm\(^3\) \(n=10\) at hour 4 \(P<0.005\) and at hour 6 \(P<0.01\) (Fig 2). Similarly, maximal concentrations of ACTH significantly differed in these subgroups \(111.08 \pm 25.37\) pg/mL versus \(44.72 \pm 7.02\) pg/mL, \(P<0.01\). However, concentrations of cortisol did not significantly differ in regard to volume of brain damage at any time studied.

Patients with infarctions in the carotid territory with involvement of the left \(n=9\) or right \(n=10\) hemisphere did not exhibit significantly different concentrations of hormones. None of the patients had lesions of the hypophysis. Values of cortisol or ACTH did not significantly differ in patients with \(n=8\) or without \(n=15\) a lesion of the hippocampus (data not shown).

**Discussion**

Serial measurements in the hyperacute phase of stroke demonstrated an early and massive activation of the HPA axis in response to ischemic stroke. A characteristic biphasic pattern of response was observed: initially, concentrations of ACTH and cortisol were concomitantly increased; in a second phase, despite a rapid decrease of ACTH levels, concentrations of cortisol remained increased. This pattern may be explained by an initially central activation of the HPA axis followed by a strong cortisol-induced suppression of ACTH levels concomitant with an increased susceptibility of the adrenal gland, thereby maintaining the elevated cortisol levels. Interestingly, a hyperresponsiveness of the adrenal gland to ACTH has recently been shown in the early postoperative recovery period.\(^{23}\)

Both the strong adrenal response in the absence of the parallel increase of ACTH and the relation to the extent of brain damage may also be explained by the action of other factors, such as proinflammatory cytokines, which are released in most types of tissue injury\(^{24}\) and possess a strong corticotropin-releasing hormone or ACTH-like activity.\(^{25-27}\)

Initial levels of ACTH were significantly increased in patients with ACS, which is consistent with earlier studies showing a relation between activation of the HPA axis and the occurrence of ACS.\(^{10-13}\) In this study, however, cortisol levels were not different in either group of patients. Similarly, only levels of ACTH at hour 4, but not later, were related to the volume of brain lesions and to scores of neurological and functional outcome. The observation that levels of ACTH but not cortisol were related to mental disorders, extent of brain damage, and outcome may indicate a central stress-induced activation of the HPA system, inducing secretion of ACTH more directly and earlier than that of cortisol as the most distal member of the HPA axis.

In this study no specific location of brain lesion responsible for dysregulation of the HPA axis in stroke could be identified. In particular, patients with or without lesions of the hippocampus, which is known to exert an inhibitory action on this neuroendocrine regulation,\(^{28}\) did not differ in regard to response of the HPA axis.

It cannot be excluded that these hormones, once released, secondarily reinforce damage of hypoxic brain tissue and thereby contribute to the cognitive disturbances. The concept of neurotoxicity of hormones of the HPA axis has been established by many in vitro and in vivo studies, which clearly show that glucocorticoids exacerbate hypoxic injury to neurons and astrocytes\(^{5-8}\) and impair glucose uptake and metabolism in the brain.\(^{29,30}\)

In conclusion, this kinetic study showed a strong activation of the HPA axis in hyperacute stroke with a characteristic biphasic pattern. Whereas the close relation of the severity of disease and volume of brain damage to initial ACTH levels indicates an early central induction of the HPA axis by cerebral ischemia, it still remains to be shown whether the persisting release of these hormones modulates the disease course.

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References


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