Twenty-four-Hour β-Endorphin Secretory Pattern in Stroke Patients

R. Franceschini, MD; C. Gandolfo, MD; A. Cataldi, MD; M. Del Sette, MD; P. Cianciosi, MD; C. Finocchi, MD; E. Rolandi, MD; T. Barreca, MD

Background and Purpose Abnormalities of hypothalamo-pituitary-adrenocortical axis function have been observed frequently in stroke patients. The aim of this study was to investigate plasma β-endorphin and cortisol 24-hour secretory patterns in patients early after stroke and in the convalescent period to evaluate a possible influence of brain damage on hormonal circadian pattern.

Methods Patients (n=15; age, 46 to 75 years) were evaluated in the first 24 hours and 10 days after hospital admission for ischemic cerebral stroke and compared with 15 age- and sex-matched normal subjects. Blood samples for β-endorphin and cortisol determination were drawn every 4 hours from 8 AM to 8 PM and every 2 hours from midnight to 6 AM.

Results Mean 24-hour β-endorphin and cortisol levels, recorded in the acute phase, were significantly higher (P<.05) than those recorded in normal subjects; circadian rhythm was not demonstrable for either hormone. In the convalescent period, plasma cortisol 24-hour mean values and circadian rhythm returned to the normal range, whereas the plasma β-endorphin 24-hour mean values and circadian rhythm did not.

Conclusions Cerebral stroke induces abnormalities of β-endorphin and cortisol circadian secretion. Whereas cortisol abnormalities are transient, those of β-endorphin last longer. The dissociation between β-endorphin and cortisol 24-hour secretory patterns might potentially serve as a marker of psychoneurological abnormalities occurring after stroke.

Key Words - β-endorphin - cortisol - circadian rhythm

Abnormalities of endocrine function, mainly regarding the hypothalamo-pituitary axis, have been observed frequently in stroke patients. In particular, absence of a sleep-related increase of growth hormone plasma levels, elevated prolactin nocturnal release, low basal thyroid-stimulating hormone levels, and impaired thyrotropin-releasing hormone–stimulated secretion of thyroid-stimulating hormone have been recorded in these patients.

Regarding hypothalamo-pituitary-adrenal axis (HPA-A) function, a hypercortisolism, also revealed by dexamethasone suppression test, has been observed, and an association between changes in cortisol levels, cognitive disturbances, and extension of motor impairment has been demonstrated. Moreover, a predictive value of plasma cortisol levels on prognosis in acute brain infarction has been recently proposed.

At present, data regarding the β-endorphin secretory pattern in stroke patients are not available. However, it is known that endogenous opioids, and in particular β-endorphin, are involved in the neural mechanisms controlling cognitive, behavioral, and motor functions. In the present study we evaluated the 24-hour plasma β-endorphin levels in a group of stroke patients during the acute phase and then compared them with those recorded in the convalescent period and in a group of healthy subjects.

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From the Departments of Internal Medicine (R.F., A.C., P.C., E.R., T.B.) and Neurology (C.G., M. Del S., C.F.), University of Genoa (Italy).

Correspondence to Professor R. Franceschini, Department of Internal Medicine, Viale Benedetto XV, n. 6, 16143 Genoa, Italy.
Clinical Details of the Study Population

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age, y</th>
<th>Sex</th>
<th>Associated Disease</th>
<th>Region(s) of the Cerebral Lesion(s)</th>
<th>Neurological Impairment</th>
<th>Vascular Classification</th>
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<td>F</td>
<td>Hypertension</td>
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<td>PACI</td>
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<td>M</td>
<td>Atrial fibrillation</td>
<td>Parietal white matter R</td>
<td>Mild L hemiparesis</td>
<td>LACI</td>
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<tr>
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<td>F</td>
<td>Atrial fibrillation, chronic bronchitis</td>
<td>Occipital, frontotemporal R, and cerebellar R</td>
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<td>POCI+PACI</td>
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<td>70</td>
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<td>TACI</td>
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<tr>
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<td>Hypertension, diabetes</td>
<td>Occipital L</td>
<td>R hemianopsia</td>
<td>POCI</td>
</tr>
</tbody>
</table>

Pt indicates patient; L, left; R, right; PACI, partial anterior circulation infarction; LACI, lacunar infarction; POCI, posterior circulation infarction; and TACI, total anterior circulation infarction.

Hormone Assay

Plasma immunoreactive β-endorphin levels were directly assayed by the immunoradiometric assay method with reagents supplied as a kit by Nichols Institute Diagnostic. The smallest detectable concentration was 8 ng/L; the intra-assay and interassay coefficients of variation (CVs) were 7% and 10%, respectively. Plasma cortisol was measured by radioimmunoassay, with reagents supplied as a kit by Farmos Diagnostica Ltd. The smallest detectable concentration was 27.6 nmol/L; the intra-assay and interassay CVs were 4% and 7%, respectively.

Statistical Analysis

Data obtained from all patients were averaged (mean±SEM) at each time point of the study and plotted (Fig 1) to obtain hormone secretion profiles. The statistical significance of the time effect on the variations observed in β-endorphin and cortisol levels was evaluated by ANOVA followed by the Tukey-Kramer multiple comparison test. The 24-hour variations in plasma β-endorphin and cortisol levels were evaluated by determining in each individual the percent CV (standard deviation of the values obtained from the 24-hour study divided by the 24-hour mean value) and the circadian excursion (CE) (highest point minus lowest point). Differences between group means were calculated by ANOVA followed by the Tukey-Kramer multiple comparison test. Data are expressed as mean±SEM.

Results

β-Endorphin Levels

In the control subjects, plasma β-endorphin levels showed significant circadian variations (F=9.918; P<.01). In the patients, plasma β-endorphin levels did not show significant circadian variations either in the acute phase (F=0.034; P>.05) or in the convalescent period (F=0.425; P>.05) (Fig 1). The 24-hour mean values recorded in the patients during the acute phase (46.1±2.3 ng/L) were higher than those recorded in the convalescent phase (35.2±1.5 ng/L; P<.01) and in the control subjects (24.7±0.9 ng/L; P<.05). The mean CV of the acute phase (18.2±2.3%) was comparable to that of the convalescent phase (21.9±2.4%) and significantly lower (P<.01) than control values (31.6±1.9%). The mean CE in the acute phase (21.0±2.1 ng/L) was not significantly different from that recorded in the
Cortisol

The 24-hour plasma cortisol values recorded in the patients during the acute phase did not show significant circadian variations (F=0.573; P>.05). Significant circadian variations were found in the control subjects (F=11.625; P<.01) and in the patients during the convalescent phase (F=9.510; P<.01) (Fig 1).

During the acute phase, the 24-hour mean values (495.7±14.6 nmol/L) were significantly higher than those recorded in the convalescent period (320.7±12.1 nmol/L; P<.01) and in control subjects (303.7±11.9 nmol/L; P<.01). The mean CV of the acute phase (16.7±1.6%) was significantly lower than that of the convalescent phase (34.9±3.9%; P<.05) and of control subjects (36.5±3.1%; P<.01). The mean CE recorded during the acute phase (232.5±23.4 nmol/L) was not significantly different from that of the convalescent period (355.1±25.7 nmol/L) and of control subjects (298.7±20.4 nmol/L). No significant differences were found between 24-hour mean cortisol values, CV, and CE recorded in patients during the convalescent phase and in control subjects (Fig 2).

Discussion

During the acute phase, in stroke patients plasma β-endorphin and cortisol 24-hour mean values were higher than those recorded in normal subjects. In addition, the physiological circadian β-endorphin and cortisol secretory rhythms were not appreciable. In the convalescent period, plasma cortisol 24-hour mean values and circadian rhythm returned to the normal range, whereas plasma β-endorphin 24-hour mean values and circadian rhythm did not.

The finding of increased plasma β-endorphin and cortisol levels in the acute phase of stroke suggests the hypothesis of a loss of cortical inhibitory control on HPA-A activity. This hypothesis agrees with previous observations showing increased cortisol basal and 24-hour plasma and urinary values in stroke patients. In particular, this finding has been recorded in association with frontal lobe damage, supratentorial lesions, and lesions involving the right hemisphere.

In our study it is noteworthy that the majority of the patients show cerebral lesions involving frontal lobes and/or right hemisphere. It may be that control of these areas on HPA-A function is mainly inhibitory and that lesions occurring there interfere with this inhibitory function. The improvement of cortisol secretion in the convalescent period, when cerebral tissue perfusion improves and a limitation of the lesion area occurs, is also in keeping with the above hypothesis. However, it must be considered that patients with acute stroke who are admitted to an intensive care unit experience stress in reaction to their own disease and to the new environment. Thus, this and other factors, such as fever,
agitation, or increased intracranial pressure, which may cause hypersecretive episodes, may obscure normal circadian rhythm and simultaneously be responsible for the increased 24-hour mean hormonal values.

Finally, it has been demonstrated that cerebral ischemia is followed by a significant increase in extracellular serotonin release. Thus, a cerebral ischemia-related stimulation of HPA-A, mediated by serotonergic pathway activation, may be hypothesized. It is known that serotonin plays a stimulatory role in HPA-A function. Indeed, our patients showed a blunted nocturnal decline of HPA-A activity. In fact, CEs of both cortisol and β-endorphin in the acute phase of stroke were lower than those observed in normal subjects, whereas CEs were comparable. Nevertheless, during the convalescent period plasma β-endorphin 24-hour mean values and circadian variations did not return to normality. This finding is difficult to explain, since it is known that corticotropin (adrenocorticotropic hormone [ACTH]), β-endorphin, and the other related peptides derive from the common precursor pro-opiomelanocortin, are released by the pituitary gland and fluctuate during the day concomitantly. However, a dissociation between plasma levels of β-endorphin and corticotropin/cortisol has been recorded in some physiological and pathological conditions, involving neurotransmitter mechanisms regulating hypothalamic-pituitary secretion. Finally, the possibility that hyperendorphinemia, which characterizes stroke patients in both the acute phase and the convalescent period, could originate outside the anterior pituitary and in particular from ischemic cerebral tissue cannot be ruled out. Experimental studies have demonstrated that ischemic brain failure after carotid artery ligation is followed by an increase of β-endorphin concentration in the ischemic hemisphere.

In conclusion, our study demonstrates an alteration of plasma β-endorphin concentrations in stroke patients, which also persists in the convalescent period. A link between the β-endorphin secretory pattern and functional outcome cannot be established with certainty by our study because of the relatively small number of cases. However, if we consider that similar changes in the β-endorphin secretory pattern occur in multi-infarct dementia, the possibility that β-endorphin secretion might potentially serve as a marker of motor, cognitive, and behavioral function after stroke may be proposed.

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References

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