Plasma α-Melanocyte Stimulating Hormone Predicts Outcome in Ischemic Stroke

Dannielle Zierath, BS; Pat Tanzi, BSN, RN, CCRC; Kevin Cain, PhD; Dean Shibata, MD; Kyra Becker, MD

Background and Purpose—α-Melanocyte stimulating hormone (α-MSH) is an endogenously produced neuropeptide derived from the same precursor as adrenocorticotropic hormone. α-MSH has profound immunomodulatory properties and may also be neuroprotective. Nothing is known about α-MSH and changes in its plasma concentrations in patients with acute ischemic stroke.

Methods—In this prospective observational study, plasma concentrations of α-MSH, adrenocorticotropic hormone, cortisol, and interleukin 6 were assessed longitudinally over the course of 1 year after stroke onset in 111 patients. Logistic regression was used to the effect of initial plasma α-MSH, adrenocorticotropic hormone, cortisol, and interleukin 6 on long-term outcome.

Results—There was an early decrease in plasma α-MSH in patients with severe stroke (National Institutes of Health Stroke Scale ≥17) that normalized over the course of the year; these same patients evidenced elevations in plasma cortisol and interleukin 6. Higher initial plasma α-MSH, but not adrenocorticotropic hormone, cortisol, or interleukin 6, was independently predictive of good long-term outcome.

Conclusions—This research is the first to study endogenous changes in plasma α-MSH after stroke. The independent effect of early plasma α-MSH on stroke outcome, as well as a growing body of experimental data demonstrating improved stroke outcome with exogenous α-MSH administration, suggests a potential therapeutic role for α-MSH in the treatment of stroke. (Stroke. 2011;42:3415-3420.)

Key Words: α-MSH ■ stroke ■ outcome
as soon as possible after stroke onset and at 3, 7, 30, 90, 180, and 365 days after stroke onset. Plasma was frozen at −80°C until use.

Clinical Data
Demographic and clinical data were collected on all of the patients. Stroke severity was determined by the National Institutes of Health Stroke Scale score and outcome by the modified Rankin Scale. Total infarct volume on initial diffusion-weighted MRI was calculated by the ABC/2 method by a single radiologist trained in the Cardiovascular Health Study and Atherosclerosis Risk in Communities protocols for infarct scoring. Information about therapeutic interventions for the treatment of stroke and stroke-related complications, such as infection, was collected. Infection was defined as clinical symptoms of an infection (fever and/or pyuria for urinary tract infection and fever and/or productive cough and radiographic evidence of consolidation for pneumonia) and positive culture data (for both pneumonia and urinary tract infection).

Laboratory Studies
Leukocyte counts, plasma cortisol, and ACTH concentrations were determined by the clinical laboratory. Plasma α-MSH concentrations were determined using a commercially available enzyme immunoassay kit (Phoenix Pharmaceuticals, Belmont, CA). Briefly, peptides were eluted from 0.5 mL of acidified plasma using C18-SEP columns containing 200 mg of C18 (Phoenix Pharmaceuticals, Belmont CA); the samples were evaporated by centrifugal vacuum concentration and reconstituted in 125 μL of buffered saline before enzyme immunoassay. The concentration of circulating IL-6 was measured with a cytometric bead-based system (Fluorokine MAP, R&D Systems); the lower limit of detection was 1.11 pg/mL. Values below the limit of detection are referred to as not detected and assigned the lowest limit of detection for statistical testing.

Statistics
Descriptive data are presented as median and interquartile range. Group comparisons were performed using the Mann-Whitney U test or Kruskal-Wallis H test. Data were normalized and associations tested using the Pearson correlation. Logistic regression was used to estimate the odds ratio and 95% CI for the effect of the highest initial α-MSH concentration (within 72 hours of stroke onset) on neurological outcome at 1, 3, 6, and 12 months after stroke onset. Given the relatively severe strokes seen in this study, good outcome was defined as independent ambulation (modified Rankin Scale ≤3). Significance was set at P≤0.05.

Results
A total of 114 patients were enrolled in the parent study; plasma α-MSH concentrations were determined in 111 of these patients,
Cortisol and ACTH lower concentrations of plasma

Publications related to this study population, we divided patients

1–80 mL), and 35% of the patients were women. As in other

(range: 4–19), the median infarct volume was 12 mL (range:

hours), the median age was 57 years (range: 44–66 years), the

onset (Figure A). There was still a trend toward decreased

least severe strokes at both 24 hours and 72 hours after stroke

significant ($P < 0.05$).

who are the subject of this article. The characteristics of the

overall study population have been described elsewhere.$^9,10$ For

the 111 patients in whom $\alpha$-MSH was assessed early (by 72

hours), the median age was 57 years (range: 44–66 years), the

median National Institutes of Health Stroke Scale score was 11

(range: 4–19), the median infarct volume was 12 mL (range:

1–80 mL), and 35% of the patients were women. As in other

publications related to this study population, we divided patients

into tertiles based on stroke severity to assess changes in plasma

$\alpha$-MSH over the course of time.$^9,10$ Patients with the most severe

strokes (National Institutes of Health Stroke Scale $\geq 17$) had

lower concentrations of plasma $\alpha$-MSH than patients with the

least severe strokes at both 24 hours and 72 hours after stroke

onset (Figure A). There was still a trend toward decreased

$\alpha$-MSH at 1 week after stroke onset in these severely affected

patients, but the differences normalized over the course of time.

At 1 year after stroke, the median $\alpha$-MSH concentration among

all of the patients was 12.8 pg/mL (range: 6.4–21.1 pg/mL),

which is similar to that reported in the literature for healthy

adults.$^{13}$ Stroke severity appeared to have little impact on plasma

ACTH (Figure B), but patients with more severe strokes evi-
denced increases in cortisol and IL-6 that persisted for $\geq 1$ month

after stroke onset (Figure C and D).

Early relationships among $\alpha$-MSH, ACTH, cortisol, and IL-6,
as well as the relationships of $\alpha$-MSH, ACTH, cortisol, and IL-6
with infarct volume and stroke severity, are displayed in Table 1.
Table 2 depicts the differences in the highest $\alpha$-MSH concentra-
tion within the first 72 hours after stroke as a function of clinical
and demographic differences between patients, none of which
are significant after controlling for stroke severity. Initial
plasma $\alpha$-MSH was not predictive of early poststroke infection
in either univariate analyses or analyses controlling for covari-
ates (data not shown).

The effect of $\alpha$-MSH, ACTH, cortisol, and IL-6 on early
and long-term outcomes is shown in Table 3. Univariate

associations between initial IL-6 and worse outcomes are
seen early after stroke (1 and 3 months), but this effect seems
to be related solely to stroke severity. Higher plasma cortisol
is independently associated with worse outcomes at 1 month
after stroke onset, but this relationship attenuates over the

course of time and is lost after controlling for stroke severity

and other important predictors of outcome. The effect of early
plasma $\alpha$-MSH concentrations on outcome was not apparent
until later time points after stroke and was independent of
initial stroke severity, patient age, and infection status.

Discussion

In this study we found early and sustained elevations in both
plasma cortisol (to 1 month) and IL-6 (to 6 months) among
patients with severe stroke, whereas ACTH concentrations
were largely unchanged and $\alpha$-MSH concentrations de-
creased early after stroke. That elevated plasma cortisol is
seen in patients with severe strokes and is associated with
worse outcome is well documented.$^{3,5,13–15}$ Increased cortisol
is considered to be a marker of the acute phase/stress response
in stroke and is variably attributed to increased ACTH and/or
IL-6.$^{16,17}$ We found both plasma cortisol and IL-6 to be highly
correlated with stroke severity and infarct volume. As might
be expected, there was a correlation between plasma ACTH
and cortisol, and this correlation was essentially unchanged
after controlling for stroke severity. Also, similar to previous
studies, we saw a correlation between IL-6 and plasma
cortisol. This correlation was slightly attenuated but not lost
after controlling for stroke severity, suggesting that IL-6 may
drive some cortisol production independent of stroke severity
and ACTH expression. Despite the common origin of $\alpha$-MSH
and ACTH from POMC, the plasma concentrations of these
neuropeptides were not correlated after stroke, and the asso-
ciation between plasma $\alpha$-MSH and stroke severity/infarct
volume was not nearly as robust as that seen for cortisol and

---

Table 1. Correlations Among $\alpha$-MSH, ACT, Cortisol, Infarct Volume, and Stroke Severity at 24 Hours and 72 Hours After Stroke Onset

<table>
<thead>
<tr>
<th>Variable</th>
<th>Infarct Volume*</th>
<th>ACTH</th>
<th>Cortisol</th>
<th>IL-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>a-MSH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td>-0.148, NS</td>
<td>-0.479, $P=0.010$</td>
<td>-0.127, NS</td>
<td>-0.501, $P=0.025$</td>
</tr>
<tr>
<td></td>
<td>-0.238, NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72 h</td>
<td>-0.247, $P=0.014$</td>
<td>-0.241, $P&lt;0.001$</td>
<td>-0.139, $P=0.181$</td>
<td>-0.115, NS</td>
</tr>
<tr>
<td></td>
<td>-0.209, $P=0.042$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td>0.498, $P=0.007$</td>
<td>0.728, $P&lt;0.001$</td>
<td>0.304, $P=0.132$</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>...</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72 h</td>
<td>0.420, $P=0.001$</td>
<td>0.616, $P&lt;0.001$</td>
<td>0.346, $P&lt;0.001$</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>...</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td>0.069, NS</td>
<td>-0.068, NS</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>...</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72 h</td>
<td>0.138, $P=0.161$</td>
<td>0.127, $P=0.193$</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>...</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td>0.517, $P=0.006$</td>
<td>0.700, $P&lt;0.001$</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>...</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72 h</td>
<td>0.393, $P&lt;0.001$</td>
<td>0.566, $P&lt;0.001$</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>
 associations between the order of minutes, it is possible that more significant
found that higher plasma H\textsubscript{9251}IL-6. Given that the half-life of H\textsubscript{9251}IL-6 in circulation is on
outcome has been documented previously.\textsuperscript{5,18} There are numerous mechanisms by which
an independent association among cortisol, IL-6, and stroke outcome has been documented previously.\textsuperscript{5,18} Both the independent association of H\textsubscript{9251}α-MSH with stroke outcome and the delay in this observed association suggest that the effect of early plasma H\textsubscript{9251}α-MSH on outcome is more than a reflection of the stress response related to stroke severity and that maintenance of plasma H\textsubscript{9251}α-MSH after stroke onset may be protective. Furthermore, a growing body of experimental data shows that exogenous administration of H\textsubscript{9251}α-MSH decreases infarct volume and improves stroke outcome.\textsuperscript{7,19–22} Potent antipyretic properties of H\textsubscript{9251}α-MSH, which could potentially be capitalized on in the treatment of stroke, are mediated through the MCR3/MCR4 melanocortin receptors (MCRs). Potent antipyretic properties of H\textsubscript{9251}α-MSH, which could potentially be capitalized on in the treatment of stroke, are mediated through the MCR3/MCR4 melanocortin receptors (MCRs). Potent antipyretic properties of H\textsubscript{9251}α-MSH, which could potentially be capitalized on in the treatment of stroke, are mediated through the MCR3/MCR4 melanocortin receptors (MCRs). Potent antipyretic properties of H\textsubscript{9251}α-MSH, which could potentially be capitalized on in the treatment of stroke, are mediated through the MCR3/MCR4 melanocortin receptors (MCRs). Potent antipyretic properties of H\textsubscript{9251}α-MSH, which could potentially be capitalized on in the treatment of stroke, are mediated through the MCR3/MCR4 melanocortin receptors (MCRs). Potent antipyretic properties of H\textsubscript{9251}α-MSH, which could potentially be capitalized on in the treatment of stroke, are mediated through the MCR3/MCR4 melanocortin receptors (MCRs). Potent antipyretic properties of H\textsubscript{9251}α-MSH, which could potentially be capitalized on in the treatment of stroke, are mediated through the MCR3/MCR4 melanocortin receptors (MCRs). Potent antipyretic properties of H\textsubscript{9251}α-MSH, which could potentially be capitalized on in the treatment of stroke, are mediated through the MCR3/MCR4 melanocortin receptors (MCRs). Potent antipyretic properties of H\textsubscript{9251}α-MSH, which could potentially be capitalized on in the treatment of stroke, are mediated through the MCR3/MCR4 melanocortin receptors (MCRs). Potent antipyretic properties of H\textsubscript{9251}α-MSH, which could potentially be capitalized on in the treatment of stroke, are mediated through the MCR3/MCR4 melanocortin receptors (MCRs). Potent antipyretic properties of H\textsubscript{9251}α-MSH, which could potentially be capitalized on in the treatment of stroke, are mediated through the MCR3/MCR4 melanocortin receptors (MCRs).
receptor complex in the brain. MCR1 is expressed by cells of the immune system and is responsible for mediating the robust anti-inflammatory and immunomodulatory properties of α-MSH, which include the prevention of T-helper 1 responses and the induction of T regulatory responses to selected antigens. Given the effect of α-MSH on the immune response, it is not surprising that it has been shown to improve outcome in animal models of experimental allergic encephalomyelitis. We also found that α-MSH administration decreased infarct volume and improved neurological outcome 24 hours after transient middle cerebral artery occlusion in an animal model of stroke. Consistent with the known effects of α-MSH on the immune response, we found that splenocytes harvested from α-MSH-treated animals responded less well to phytohemagglutinin (a lymphocyte mitogen) than splenocytes harvested from saline-treated animals. Furthermore, the animals treated with α-MSH in this study were less likely to develop autoimmune responses to myelin basic protein, a response associated with worse stroke outcome. Finally, α-MSH has neurotrophic properties that could aid in stroke recovery. At least some of these neurotrophic effects appear to be mediated by MCR4. These effects of α-MSH, along with the immunomodulatory effects, may help to explain why delayed administration of α-MSH can improve outcome and why the association between early α-MSH and stroke outcome is not apparent until later time points. 

α-MSH is an attractive candidate for stroke therapy given its multiplicity of actions and the possibility that delayed administration may still be of therapeutic value. The attractiveness of α-MSH as a therapeutic agent is further enhanced by its potential ease of administration; MSH-related neuropeptides are absorbed through the nasal mucosa rapidly after inhalation. In addition to exogenous administration of the neuropeptide, plasma α-MSH concentrations could be augmented by strategies that favor α-MSH processing from POMC/ACTH (ie, enhancing PC2 activity). The potent immunomodulatory properties of α-MSH, however, suggest the possibility that this peptide could predispose to infection, a complication that was seen in an animal model of stroke. In the current study, however, we did not find an independent association between α-MSH and infection risk. Furthermore, we did not see infectious complications related to α-MSH administration in our animal model of stroke.

Limitations of this study include the lack of tightly controlled timing of blood draws early after stroke onset. The median time from stroke onset to the “24-hour” blood draw was 28 hours (N=30), whereas the median time from stroke onset to the “72-hour” blood draw was 68 hours (N=101). It is certainly possible that rapid changes in plasma α-MSH were missed by this sampling protocol. For the logistic regression, we chose to use the highest α-MSH (ACTH, cortisol, and IL-6) in the first 72 hours of stroke onset to increase statistical power (if only the 72-hour values are used, the results are similar but not quite as significant). The statistics were not corrected for multiple comparisons; results should, therefore, be interpreted as hypothesis generating.

In summary, decreased plasma α-MSH is seen early after stroke onset in patients with severe stroke. In addition, higher

Table 3. Likelihood for a Good Outcome at Given Time Points Based on Initial Plasma α-MSH or Cortisol

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model</th>
<th>mRS ≤3</th>
<th>P</th>
<th>mRS ≤3</th>
<th>P</th>
<th>mRS ≤3</th>
<th>P</th>
<th>mRS ≤3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mo, N=102</td>
<td>Unadjusted</td>
<td>1.355 (0.938–1.957)</td>
<td>0.105</td>
<td>0.852 (0.676–1.075)</td>
<td>0.176</td>
<td>0.169 (0.075–0.381)</td>
<td>&lt;0.001</td>
<td>0.583 (0.389–0.874)</td>
<td>0.009</td>
</tr>
<tr>
<td>NHSS</td>
<td>1.031 (0.694–1.531)</td>
<td>NS</td>
<td>0.921 (0.688–1.232)</td>
<td>NS</td>
<td>0.394 (0.158–0.986)</td>
<td>0.047</td>
<td>0.896 (0.633–1.269)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>NHSS+age</td>
<td>1.000 (0.667–1.499)</td>
<td>NS</td>
<td>0.931 (0.698–1.241)</td>
<td>NS</td>
<td>0.389 (0.153–0.988)</td>
<td>0.047</td>
<td>0.915 (0.643–1.302)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>NHSS+age+infection</td>
<td>0.991 (0.657–1.494)</td>
<td>NS</td>
<td>0.940 (0.693–1.274)</td>
<td>NS</td>
<td>0.392 (0.154–0.998)</td>
<td>0.049</td>
<td>0.940 (0.661–1.337)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>3 mo, N=100</td>
<td>Unadjusted</td>
<td>2.147 (1.159–3.978)</td>
<td>0.015</td>
<td>0.840 (0.659–1.070)</td>
<td>0.157</td>
<td>0.299 (0.154–0.581)</td>
<td>&lt;0.001</td>
<td>0.556 (0.375–0.825)</td>
<td>0.004</td>
</tr>
<tr>
<td>NHSS</td>
<td>1.639 (0.883–3.043)</td>
<td>0.118</td>
<td>0.880 (0.657–1.180)</td>
<td>NS</td>
<td>0.657 (0.307–1.405)</td>
<td>NS</td>
<td>0.755 (0.518–1.102)</td>
<td>0.145</td>
<td></td>
</tr>
<tr>
<td>NHSS+age</td>
<td>1.568 (0.844–2.911)</td>
<td>0.154</td>
<td>0.896 (0.678–1.183)</td>
<td>NS</td>
<td>0.664 (0.300–1.467)</td>
<td>NS</td>
<td>0.752 (0.503–1.123)</td>
<td>0.163</td>
<td></td>
</tr>
<tr>
<td>NHSS+age+infection</td>
<td>1.688 (0.859–3.319)</td>
<td>0.129</td>
<td>0.923 (0.682–1.248)</td>
<td>NS</td>
<td>0.721 (0.311–1.669)</td>
<td>NS</td>
<td>0.792 (0.530–1.183)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>6 mo, N=97</td>
<td>Unadjusted</td>
<td>5.212 (1.614–16.834)</td>
<td>0.006</td>
<td>0.736 (0.560–0.969)</td>
<td>0.029</td>
<td>0.368 (0.178–0.759)</td>
<td>0.007</td>
<td>0.877 (0.738–1.042)</td>
<td>0.136</td>
</tr>
<tr>
<td>NHSS</td>
<td>4.219 (1.225–14.530)</td>
<td>0.023</td>
<td>0.741 (0.533–1.032)</td>
<td>0.076</td>
<td>0.724 (0.300–1.747)</td>
<td>NS</td>
<td>1.033 (0.855–1.248)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>NHSS+age</td>
<td>4.236 (1.191–15.063)</td>
<td>0.026</td>
<td>0.729 (0.534–0.996)</td>
<td>0.047</td>
<td>0.662 (0.254–1.727)</td>
<td>NS</td>
<td>1.030 (0.852–1.246)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>NHSS+age+infection</td>
<td>5.763 (1.350–24.591)</td>
<td>0.018</td>
<td>0.737 (0.537–1.011)</td>
<td>0.059</td>
<td>0.677 (0.257–1.784)</td>
<td>NS</td>
<td>1.050 (0.863–1.278)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>12 mo, N=96</td>
<td>Unadjusted</td>
<td>4.444 (1.322–14.943)</td>
<td>0.016</td>
<td>0.674 (0.427–1.003)</td>
<td>0.081</td>
<td>0.464 (0.215–1.000)</td>
<td>0.050</td>
<td>0.873 (0.734–1.039)</td>
<td>0.125</td>
</tr>
<tr>
<td>NHSS</td>
<td>3.551 (1.034–12.201)</td>
<td>0.044</td>
<td>0.922 (0.631–1.325)</td>
<td>0.146</td>
<td>0.937 (0.355–2.473)</td>
<td>NS</td>
<td>1.006 (0.831–1.218)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>NHSS+age</td>
<td>3.502 (0.991–12.370)</td>
<td>0.052</td>
<td>0.920 (0.625–1.354)</td>
<td>NS</td>
<td>0.859 (0.288–2.563)</td>
<td>NS</td>
<td>0.998 (0.820–2.125)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>NHSS+age+infection</td>
<td>4.612 (1.087–19.572)</td>
<td>0.038</td>
<td>0.933 (0.630–1.381)</td>
<td>NS</td>
<td>0.933 (0.294–2.955)</td>
<td>NS</td>
<td>1.012 (0.826–1.240)</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as the odds ratio (95% CI) per 10-pg/mL increase in plasma α-MSH, ACTH, and IL-6 concentrations or 10-μg/dL increase in cortisol concentration.

Data show the highest plasma α-MSH, ACTH, cortisol, or IL-6 within the first 72 h after stroke.

α-MSH indicates melanocyte stimulating hormone; ACTH, adrenocorticotrophic hormone; IL, interleukin; NIHSS, National Institutes of Health Stroke Scale; NS, not significant (P=0.200); CI, confidence interval.
concentrations of plasma α-MSH are independently associated with better stroke outcome. These data, along with a robust body of experimental data, suggest that strategies to increase α-MSH may be a viable therapeutic intervention for the treatment of acute ischemic stroke and should be further investigated.

Sources of Funding

This work was supported in part by NINDS R01NS049197.

None.

Disclosures

References

Plasma α-Melanocyte Stimulating Hormone Predicts Outcome in Ischemic Stroke
Dannielle Zierath, Pat Tanzi, Kevin Cain, Dean Shibata and Kyra Becker

Stroke. 2011;42:3415-3420; originally published online September 29, 2011;
doi: 10.1161/STROKEAHA.111.627331
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/42/12/3415

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2012/08/21/STROKEAHA.111.627331.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/
血液中α-メラニン細胞刺激ホルモン濃度は虚血性脳卒中の転帰を予測する

Plasma α-Melanocyte Stimulating Hormone Predicts Outcome in Ischemic Stroke

Dannielle Zierath, BS1; Pat Tanzi, BSN, RN, CCRC1; Kevin Cain, PhD2; Dean Shibata, MD3; Kyra Becker, MD1

Departments of 1Neurology, 2Biostatistics, and 3Radiology, University of Washington School of Medicine, Harborview Medical Center, Seattle, WA.

背景および目的：α-メラニン細胞刺激ホルモン（α-MSH）は、内因的に生成される神経ペプチドで、副腎皮質刺激ホルモンと同じ前駆体に由来する。α-MSHは、類性免疫調節作用を加え、神経保護作用を有する可能性がある。しかし、急性虚血性脳卒中患者におけるα-MSHおよびその血漿中濃度の変化については知られていない。

方法：本研究は、虚血性脳卒中急性期を発症した111例において、α-MSH、副腎皮質刺激ホルモン、コルチゾール、およびインターロイキン6の血漿中濃度を、脳卒中発症から1年間にわたって長期的に評価した。α-MSH、副腎皮質刺激ホルモン、コルチゾール、およびインターロイキン6の初期血漿中濃度が長期的転帰に及ぼす影響をロジスティック回帰分析した。

結果：重度の脳卒中（NIHSS ≥ 17）患者において、血漿中α-MSH濃度は早期に低下し、1年間で正常化した。同患者群において、血漿中コルチゾールおよびインターロイキン6濃度が上昇した。初期の血漿中α-MSHが高値で、かつ副腎皮質刺激ホルモン、コルチゾール、およびインターロイキン6が高価でないことは、良好な長期的転帰の独立した予測因子であった。

結論：本研究は、脳卒中後期の血漿中α-MSH濃度の内因性変化を検証した研究である。初期の血漿中α-MSH濃度の脳卒中転帰に対する独立した効果が示され、また、外因性α-MSHの投与により脳卒中の転帰が改善することを示す実験データが増加していることから、脳卒中治療におけるα-MSHの治療的役割の可能性が示唆される。

表3 初期血漿中α-MSHまたはコルチゾール濃度に基づく各時点での良好な転帰の尤度

<table>
<thead>
<tr>
<th>変数</th>
<th>モデル</th>
<th>α-MSH mRS ≤3 p 値</th>
<th>ACTH mRS ≤3 p 値</th>
<th>コルチゾール mRS ≤3 p 値</th>
<th>IL-6 mRS ≤3 p 値</th>
</tr>
</thead>
<tbody>
<tr>
<td>1週, 102例</td>
<td>補正前</td>
<td>1.355(0.938~1.957) 0.105</td>
<td>0.852(0.676~1.075) 0.176</td>
<td>0.169(0.075~0.381) &lt;0.001</td>
<td>0.583(0.389~0.874) 0.009</td>
</tr>
<tr>
<td>NIHSS</td>
<td>1.031(0.694~1.531) NS</td>
<td>0.921(0.688~1.232) NS</td>
<td>0.394(0.158~0.986) 0.047</td>
<td>0.896(0.633~1.269) NS</td>
<td></td>
</tr>
<tr>
<td>NIHSS+年齢</td>
<td>1.000(0.667~1.499) NS</td>
<td>0.931(0.698~1.241) NS</td>
<td>0.389(0.153~0.988) 0.047</td>
<td>0.915(0.643~1.302) NS</td>
<td></td>
</tr>
<tr>
<td>NIHSS+年齢 +感染症</td>
<td>0.991(0.657~1.494) NS</td>
<td>0.940(0.693~1.274) NS</td>
<td>0.392(0.154~0.998) 0.049</td>
<td>0.940(0.661~1.337) NS</td>
<td></td>
</tr>
<tr>
<td>3週, 100例</td>
<td>補正前</td>
<td>2.147(1.159~3.978) 0.015</td>
<td>0.840(0.659~1.070) 0.157</td>
<td>0.299(0.154~0.581) &lt;0.001</td>
<td>0.556(0.375~0.825) 0.004</td>
</tr>
<tr>
<td>NIHSS</td>
<td>1.639(0.883~3.043) 0.118</td>
<td>0.880(0.657~1.180) NS</td>
<td>0.657(0.307~1.405) NS</td>
<td>0.755(0.518~1.102) 0.145</td>
<td></td>
</tr>
<tr>
<td>NIHSS+年齢</td>
<td>1.568(0.844~2.911) 0.154</td>
<td>0.896(0.678~1.183) NS</td>
<td>0.664(0.300~1.467) NS</td>
<td>0.752(0.503~1.123) 0.163</td>
<td></td>
</tr>
<tr>
<td>NIHSS+年齢 +感染症</td>
<td>1.688(0.859~3.319) 0.129</td>
<td>0.923(0.682~1.248) NS</td>
<td>0.721(0.311~1.669) NS</td>
<td>0.792(0.530~1.183) NS</td>
<td></td>
</tr>
<tr>
<td>6週, 97例</td>
<td>補正前</td>
<td>5.212(1.614~16.834) 0.006</td>
<td>0.736(0.560~0.969) 0.029</td>
<td>0.368(0.178~0.759) 0.007</td>
<td>0.877(0.738~1.042) 0.136</td>
</tr>
<tr>
<td>NIHSS</td>
<td>4.219(1.225~14.530) 0.023</td>
<td>0.741(0.533~1.032) 0.076</td>
<td>0.724(0.300~1.747) NS</td>
<td>1.033(0.855~1.248) NS</td>
<td></td>
</tr>
<tr>
<td>NIHSS+年齢</td>
<td>4.236(1.191~15.063) 0.026</td>
<td>0.729(0.534~0.996) 0.047</td>
<td>0.662(0.254~1.727) NS</td>
<td>1.030(0.852~1.246) NS</td>
<td></td>
</tr>
<tr>
<td>NIHSS+年齢 +感染症</td>
<td>5.763(1.350~24.591) 0.018</td>
<td>0.737(0.537~1.011) 0.059</td>
<td>0.677(0.257~1.784) NS</td>
<td>1.050(0.863~1.278) NS</td>
<td></td>
</tr>
<tr>
<td>12週, 96例</td>
<td>補正前</td>
<td>4.444(1.322~14.943) 0.016</td>
<td>0.874(0.657~1.163) NS</td>
<td>0.464(0.215~1.000) 0.050</td>
<td>0.873(0.734~1.039) 0.125</td>
</tr>
<tr>
<td>NIHSS</td>
<td>3.551(1.034~12.201) 0.044</td>
<td>0.922(0.683~1.245) NS</td>
<td>0.937(0.355~2.473) NS</td>
<td>1.006(0.831~1.218) NS</td>
<td></td>
</tr>
<tr>
<td>NIHSS+年齢</td>
<td>3.502(0.991~12.370) 0.052</td>
<td>0.920(0.625~1.354) NS</td>
<td>0.859(0.288~2.563) NS</td>
<td>0.998(0.820~1.215) NS</td>
<td></td>
</tr>
<tr>
<td>NIHSS+年齢 +感染症</td>
<td>4.612(1.087~19.572) 0.038</td>
<td>0.933(0.630~1.381) NS</td>
<td>0.933(0.294~2.955) NS</td>
<td>1.012(0.826~1.240) NS</td>
<td></td>
</tr>
</tbody>
</table>

データは、血漿中α-MSH、ACTH、およびIL-6濃度の10pg/mL上昇またはコルチゾール濃度10μg/dL上昇あたりのオッズ比（95％CI）で表示。データは脳卒中後72時間以内の最高血漿中α-MSH、ACTH、コルチゾール、またはIL-6濃度を示す。

MSH: メラニン細胞刺激ホルモン、ACTH: 副腎皮質刺激ホルモン、IL: インターロイキン、NIHSS: 国立衛生研究所脳卒中スケール、NS:有意差なし（p ≥ 0.200）、CI: 信頼区間。