Transcerebral Exchange Kinetics of Nitrite and Calcitonin Gene-Related Peptide in Acute Mountain Sickness Evidence Against Trigeminovascular Activation?

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Background and Purpose—High-altitude headache is the primary symptom associated with acute mountain sickness, which may be caused by nitric oxide-mediated activation of the trigeminovascular system. Therefore, the present study examined the effects of inspiratory hypoxia on the transcerebral exchange kinetics of the vasoactive molecules, nitrite (NO$_2$), and calcitonin gene-related peptide (CGRP). These findings argue against sustained trigeminovascular system activation as a significant event in acute mountain sickness. (Stroke. 2009;40:00-00.)

Key Words: acute mountain sickness ■ brain ■ calcitonin gene-related peptide ■ hypoxia ■ gene-related peptide ■ nitrite

Materials and Methods

Subjects and Design
Ten healthy males aged 27 (mean)±4 (SD) years without any history of headache, migraine, or AMS provided written informed consent following approval by the Scientific Ethics Committee of Copenhagen and Frederiksberg Municipalities (Denmark). Catheters were placed under local anesthesia in the radial artery and the right internal jugular vein via ultrasound guidance with the tip pointing cranially. After 30 minutes of supine rest, measurements were obtained in normoxia (21% O$_2$), and measurements were obtained after 9 hours of passive exposure to normobaric hypoxia (12.9% O$_2$).

Results—Hypoxia increased cerebral blood flow with a corresponding increase in acute mountain sickness and headache scores ($P<0.05$ vs normoxia). Hypoxia blunted the cerebral uptake of NO$_2$, whereas CGRP exchange remained unaltered. No relationships were observed between the change (hypoxia–normoxia) in cerebral NO$_2$ or CGRP exchange and acute mountain sickness/headache scores ($P>0.05$).

Conclusion—These findings argue against sustained trigeminovascular system activation as a significant event in acute mountain sickness.
Cerebral Hemodynamics

Hemoglobin (Hb), hematocrit (Hct), partial pressures of oxygen, carbon dioxide (P O2/PaCO2), and oxyhemoglobin saturation (SO2) were determined using a blood gas analyzer (ABL 715 Radiometer). Global cerebral blood flow (CBF) was measured using the Kety-Schmidt technique in the desaturation mode using 5% nitrous oxide for hypocapnia during the hypoxic challenge, absolute CBF values were also normalized for the cerebral vasoconstrictive effects of hypocapnia using the most accurate, precise, sensitive, specific, and validated radioimmunoassay currently available with an intra and interassay CV of 12%. To normalize for changes in PaCO2, CBFHYPOXIA was adjusted for condition + sample site interaction effect:

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\text{Adjusted CBF}_{HYPOXIA} = \frac{\text{measured CBF}_{HYPOXIA}}{[1 + (\text{PaCO2}_{HYPOXIA} - \text{PaCO2}_{NORMOXIA}) \times 0.03)]}
\]

Global cerebral plasma flow (CPF) was calculated as CBF/(1–Hct), and cerebral O2 delivery as CBF×arterial oxygen content [1.39 (Hb)×(SO2/100)+(0.003×P O2)].

Metabolic Measurements

Blood was centrifuged at 600g (4°C) for 10 minutes and K-EDTA plasma injected into tri-iodide reagent for the measurement of NO2 via ozone-based chemiluminescence with an intra and interassay CV of 7% and 10%, respectively (detection limit <1 nmol/L) based on data collected in healthy volunteers. Plasma CGRP was analyzed using the most accurate, precise, sensitive, specific, and validated radioimmunoassay currently available with an intra and interassay CV of 2% and 7% (detection limit <1 pmol/L) based on healthy volunteers. In our experience, these techniques yield normative (radial) arterial and (jugular) venous concentrations of NO2 and CGRP that range between 0.42–0.44 and 0.14, respectively, and corresponding CPF tended to increase, thus preserving cerebral O2 delivery.

Cephalalgia

AMS was assessed using the Lake Louise and Environmental Symptoms Questionnaire Cerebral scoring systems and a visual analogue scale was used to examine headache as previously described. Statistical Analysis

Shapiro-Wilk W tests confirmed distribution normality. Data were analyzed with a 2-way repeated measures analysis of variance (condition×sample site) with post hoc Bonferroni-corrected paired samples t tests. Relationships were analyzed using a Pearson Product Moment Correlation. Significance was established at P<0.05 and values are presented as mean±SD.

Results

Cerebral Hemodynamics

Hypoxia resulted in marked arterial hypoxemia as reflected by a reduction (P<0.05 vs normoxia) in PaO2, Pa CO2, and PaCO2 (Table 1). Global CBF (absolute and PaCO2-adjusted values) and corresponding CPF tended to increase, thus preserving cerebral O2 delivery.

Cerebral Metabolic Exchange

Cerebral metabolic exchange was unremarkable (Figure, C and D). Hypoxia blunted the cerebral uptake of NO2 attributable primarily to a decrease in arterial delivery, whereas no changes were observed in systemic or cerebral CGRP metabolism.

Discussion

These findings fail to support our original hypothesis and contrast with some of the observations reported in the migraine (without aura) literature, a complication of the central nervous system that shares phenotypic characteristics that are virtually indistinguishable from those encountered in AMS. Goadsby et al 14 were the first to document increased CGRP levels in the external jugular venous blood of patients during migraine attack, a finding that has since been replicated in cubital venous15 and internal jugular venous16 blood. Furthermore, CGRP infusion causes migraine-like head-
ache,17 and antagonism with BIBN 4096 BS provides effective prophylaxis.18 However, these findings have not been consistently reproduced caused, in part, by weak experimental design using historic control subjects and technical deficiencies associated with the accurate measurement of CGRP. Using an intrapatient comparative design and a more sensitive radioimmunoassay, a recent study failed to confirm any difference in CGRP levels from cubital and external jugular venous blood of patients during and outside of migraine attack without aura.11 This agrees with our current findings that adopted a similar experimental approach specifically designed to minimize the considerable interindividual variation associated with resting levels of CGRP. Incorporation of a homogenous group of apparently healthy males in the resting state excluded the potential confounding influence and interpretive complications associated with differences in sex, age, arterial hypertension, pregnancy, contraceptive pill use, and exercise on resting CGRP levels.11 Thus, we remain confident that the lack of CGRP output across the brain reflects the true physiological response to hypoxia and is not an artifact caused by methodological limitations.

However, because the half-life of CGRP has been estimated at only a few minutes,19 we cannot exclude acute release from trigeminal perivascular nerve fibers, the site of migraine nociception, during the initial early phase of hypoxia. It is conceivable that the decreased arterial delivery of NO2 may reflect an increase in the systemic rate of NO2 reduction by deoxyhemoglobin to increase the intravascular pool of bioavailable NO2 (Hb-Fe2+/NO2− → Hb-Fe3+/NO + OH−). The increase in NO may not only serve as a countermeasure to effect cerebral vasodilatation to preserve oxidative metabolism in the face of prevailing hypoxemia but may have also stimulated focal CGRP synthesis and release resulting in neurogenic vasodilatation, inflammation, hyperalgesia, and allodynia.20 Alternatively, the blood–brain barrier, which we have shown to remain mostly intact during hypoxia,13 may have also prevented intrathecally formed CGRP from entering the extracranial circulation in sufficient amounts to permit molecular detection. However, what is apparent from the current findings is that the lack of CGRP exchange at 9 hours excludes sustained steady-state release of CGRP as the primary cause of AMS. Because accumulating evidence suggests that CGRP is considered a biological marker of peripheral trigeminal vascular system activation, our findings suggest that alternative mechanisms are likely responsible for the high-altitude headache observed in AMS.
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Disclosure
None.

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