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ORIGINAL RESEARCH

Plasma proANP$_{1\text{-}98}$ Response During High Altitude Stress: Effect of Age and Ethnicity

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Objective.—Acclimatization to high altitude (HA) is accompanied by decrease in plasma atrial natriuretic peptide (ANP). On the other hand, circulating levels of the hormone are known to be influenced by age and ethnicity. The impact of these factors on ANP response during prolonged HA exposure remains unexplored. Hence, this study was conducted to examine possible age and ethnic variation in plasma proANP$_{1\text{-}98}$ levels in men after 3 to 4 weeks at HA.

Methods.—Lowlanders (LL) were studied at sea level (SL) and after 3 to 4 weeks at an altitude of ~4500 m. The LL group comprised Rajput (n = 48), Gorkha (n = 40), and South Indian (n = 43) ethnicities. Another group of HA natives (Ladakhi, n = 40) were studied at ~4500 m only. Subjects were between 20 and 50 years of age. Estimation of plasma proANP$_{1\text{-}98}$ and biochemical, hematologic, and physiologic evaluation was done.

Results.—In LL at HA, proANP$_{1\text{-}98}$ levels decreased ($P < .001$); plasma arginine vasopressin decreased ($P < .05$ in Rajputs and South Indians); and total protein, hemoglobin, and hematocrit increased ($P < .05$). Heart rate increased ($P < .05$), whereas arterial oxygen saturation decreased ($P < .05$) in all LL at HA. Ethnicity but not age variation in proANP$_{1\text{-}98}$ was observed under HA stress. In HA natives, plasma proANP$_{1\text{-}98}$ was higher than LL at HA and did not exhibit any age variation.

Conclusions.—Plasma proANP$_{1\text{-}98}$ levels, reflecting medium-term ANP secretion, decrease during prolonged exposure to HA in LL. This is due to diuresis leading to plasma volume reduction that occurs during the acclimatization process. Ethnicity but not age variation is associated with plasma proANP$_{1\text{-}98}$ under HA stress.

Key words: proatrial natriuretic peptide, men, chronic hypoxia, high altitude

Introduction

Hypoxia is a known secretagogue for atrial natriuretic peptide (ANP) and enhances ANP gene expression in mammals.[1] Atrial natriuretic peptide is primarily secreted from atrial cardiomyocytes.[2] Cleavage of proANP (1-126), the predominant storage form of ANP in atrial granules, releases equimolar amounts of the biologically active peptide ANP (99-126) and proANP (1-98), the major circulating N-terminal ANP (proANP$_{1\text{-}98}$), into the circulation.[3] For diagnostic accuracy and prognostic relevance, estimation of plasma proANP$_{1\text{-}98}$ has been suggested as a good reliable measure to measure of ANP as it is more stable ex vivo, has a longer plasma half-life, and, consequently, higher plasma concentrations (10 to 50 times) than ANP.[2] Hence, proANP$_{1\text{-}98}$ is more likely to reflect medium-term ANP secretion. Atrial natriuretic peptide release during hypoxia plays an important role in decreasing pulmonary arterial pressure (PAP), increasing fluid shift out of the circulation, and facilitating action of erythropoietin.[4] However, subjects acclimating normally have little or no change in ANP, and it has been suggested that ANP may be triggered in pathologic conditions in which natriuresis is impaired.[5–7] In high altitude natives (HANs), Antezana et al[8] have observed that plasma ANP level was less than that in sea level (SL) natives despite high PAP. However, ANP level in Ladakhis who are HANs of the Himalayas is not known, and it has been reported that pulmonary circulation in the Himalayan people is well adapted and better than that of the Andean people.[9]

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Apart from various environmental and psychological factors, levels of plasma hormones are also influenced by age and exhibit ethnic variation. This may also affect the response to stress. The Framingham Study was the first to identify that plasma natriuretic peptide levels exhibit heritability and genetic linkage along with age variations in humans.[10] Age-associated increase in plasma ANP and $proANP_{1-98}$ has been well documented.[2,10] Furthermore, aging-associated physiologic alterations in factors affecting ANP release such as PAP in hypoxia have been observed in both humans[11] and animals.[12] Some studies have reported the association between ANP gene polymorphisms and plasma ANP levels/$proANP_{1-98}$ levels, hypertension, cardiac hypertrophy, proteinuria, stroke, and recurrent stroke.[10,13] In this perspective, it is possible that variations in $proANP_{1-98}$ levels in men from different ethnic background across various age groups may be different under high altitude (HA) stress thereby modulating the adaptive processes. Also, studies concerning the influence of age on chronic hypoxia-induced structural and functional alterations in the cardiovascular system are very few and controversial.[14] With respect to the Indian population, age and ethnic variations in $proANP_{1-98}$ levels under HA stress have not been studied previously. This population is characterized by high levels of endogamy and a high degree of genetic differentiation among various ethnic groups.[15] The purpose of this report was to explore these issues by presenting data on morning plasma $proANP_{1-98}$ levels in lowlanders of different age groups and ethnicities at HA as compared with that at SL and to compare $proANP_{1-98}$ response in lowlanders with that of HANs at HA.

Materials and methods

SUBJECTS

Healthy male subjects from the armed forces ($n = 171$) between 20 and 50 years of age were enrolled for the study after informed consent and approval from the ethics committee of the institute. Subjects were chosen from four ethnically distinct groups based on geographic zones and morphologic types[16]: Rajput, Gorkha, South Indian, and Ladakhi. Rajputs are from northwestern India (Rajasthan) with Caucasoid features; Gorkhas are basically from submountainous regions (2000 to 3000 m) from northern India with Mongoloid features, and they had been living at SL for ~4 years prior to the study; and South Indians are people from the southern plains and coastal areas of the country with Australoid features. Ladakhis are HANs from Ladakh of the Himalayas, which is located with the Karakoram to the northwest, the Himalayas in the southwest, and the Trans-Himalayas at its core. High-altitude natives living at HA had never been to SL. The subjects of Rajput, Gorkha, and South Indian ethnicities are referred to as lowlanders. Subjects were categorically divided into 4 age groups (years): 20 to 24, 25 to 29, 30 to 34, and 35 to 50.

STUDY PROTOCOL

All subjects of lowland origin were evaluated at SL. These subjects were inducted to an altitude of 3500 m where they stayed for 7 days. Then, they were inducted to a higher altitude: ~4500 m for Rajputs and South Indians and ~4400 m for Gorkhas, where they continued to stay. At this final altitude, the lowland subjects were evaluated after 3 to 4 weeks of stay. Another group of HANs were studied at ~4500 m only.

DIET

Diet consisted of authorized rations of the Indian Army that included an average intake of 13 819 kJ (carbohydrate 61%, lipid 26%, protein 13%) at SL and 14 657 kJ (carbohydrate 60%, lipid 28%, protein 12%) for HA operations.[17] Food was consumed at the common mess at respective locations and is essentially the same for all subjects. Salt content in the ration was 14 to 19g.[18] There was no fluid restriction during the study.

ANTHROPOMETRY

Body weight and height were measured using an electronic weighing machine (Delmer, India) and an anthropometer. Height was measured to the nearest 0.5 cm and weight to the nearest 0.5 kg. Body fat was estimated indirectly by calculating body mass index (BMI): body weight (kg) divided by the height squared (m^2).

SAMPLE ANALYSIS

In all the subjects, fasting venous blood samples were collected between 0700 and 0800 hours. The subjects were rested for half an hour in a sitting position and then for 5 minutes in a supine position before blood drawing from the antecubital vein. Samples collected in ethylenediamine tetraacetic acid (EDTA) tubes were centrifuged, and plasma was stored at −80°C until analysis.

BIOCHEMICAL PARAMETERS

Plasma $proANP_{1-98}$ level (nmol/L) was measured by enzyme-immunoassay method (Biomedica Gruppe, Austria; code BI-20892). This kit is suitable for the use of EDTA plasma. It is recommended for stability of the