PRELIMINARY REPORT

Modification of the Responses of Endothelin-1 to Exhaustive Physical Exercise Under Simulated High-Altitude Conditions With Acute Hypoxia

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To assess whether acute alveolar hypoxia leads to the release of endothelin-1 (ET) in vivo, ET, cortisol (CORT), and lactate (LA) levels were determined in 15 healthy subjects at rest and during exhaustive incremental cycle ergometry on two separate test days. The subjects were to breathe a gas mixture with reduced O_2 content ([H] fraction of inspired O_2, 0.14) on one day and normal air on the other (N). Modified responses of LA and CORT to exhaustive incremental cycle ergometry on the H day indicated elevated anaerobic tissue metabolism and increased physical stress. With acute alveolar hypoxia, the response of ET to exhaustive physical labor was found to be augmented.

IN VITRO HYPOXIA can lead to a contraction of the smooth muscles of blood vessels.[1] This can also be mediated by the peptide endothelin-1 (ET).[2] In addition, an augmented secretion of steroids from the adrenal glands after application of the peptide was recorded in vitro,[3] as well as higher levels of ET after administration of corticotropin,[4] indicating an interrelation between the peptide's release and the endocrine reaction to stress. However, it is still controversial as to whether in vivo acute hypoxia alone leads to the release of ET in man or whether additional influence, such as physical stress are necessary.

This study therefore examines the behavior of ET at rest and the potential modifications of the peptide's response to exercise with acute hypoxia in vivo.

SUBJECTS AND METHODS

Experiments were conducted on 2 separate test days with subjects breathing in random order either regular air ([N] fraction of inspired O_2, 0.21) or a gas mixture with reduced oxygen content ([H] fraction of inspired O_2, 0.14; ≅ 3,000 m). ET, cortisol (CORT), lactate (LA), and blood gas levels were determined in 15 healthy male volunteers (age, 26.2 ± 2.8 years; height, 181.0 ± 4.7 cm; mass, 73.5 ± 10.3 kg) under fasting conditions at rest on either test day. Additional measurements were made during incremental bicycle exercise in a supine position at 100 W, 150 W, and on cessation of exercise (N, 227 ± 36 W; H, 200 ± 32 W).

Blood gas levels were determined in capillary blood from the hyperemized earlobe using a polarographic blood gas analyzer (Ciba-Corning 288, Dietlikon, Switzerland). For ET determination, blood from the cubital vein taken through an indwelling catheter was collected in ice-chilled EDTA-coated tubes and centrifuged at 1,500*g* for 20 minutes, and the plasma was frozen at −70°C until analysis. ET was extracted via SepPak C18 cartridges (Waters, Millipore, Marlboro, MA) and measured with an endothelin-sensitive radioimmunoassay (Biomedica, Vienna, Austria). The intraassay variance of the assay was 10%, and interassay variance was 16%. The ET antibody has a cross-reactivity of less than 1% with its precursor big endothelin, C-terminal hexapeptide, or sarofotoxin. CORT was determined using a commercially available radioimmunoassay (Travenol Baxter, Munich, Germany), and LA levels were measured enzymatically in capillary blood. To achieve a sensitive detection of even small modifications of the responses of the above variables to physical exercise alone or in combination with acute hypoxia, differences between the measurements at rest and those performed during ergometry were calculated. Data are presented as the mean ± SEM. Since the data were not generally normally distributed, both the resting measurements and those values pertaining to the changes associated with physical labor performed at 100 W, 150 W, and on volitional exhaustion were compared between H and N with Wilcoxon's matched-pairs signed-rank tests. The level of statistical significance was set at $\alpha = .05$.

RESULTS

With normal blood gas measurements under N, marked acute arterial hypoxia was seen on the H day at rest (PaO_2, 50.6 ± 2.07 mm Hg) and during exercise. The resting values for ET were 5.01 ± 0.22 pg · mL^{-1} with H and 5.47 ± 0.25 with N. For CORT, they were 19.6 ± 1.6 μg · dL^{-1} with H and 21.0 ± 2.32 with N. For LA, they were 0.86 ± 0.07 mmol · L^{-1} with H and 1.04 ± 0.07 with N. All resting measurements were within normal limits and did not differ between H and N.

For ET, the changes relative to the resting values on the 100-W step were +0.10 ± 0.160 pg · mL^{-1} with H and +0.008 ± 0.289 with N ($P < .001$). On the 150-W step, they were +0.183 ± 0.144 pg · mL^{-1} with H and −0.58 ± 0.248 with N ($P < .05$). On volitional exhaustion, they were +0.33 ± 0.227 pg · mL^{-1} with H and −0.415 ± 0.401 with N. For CORT, the respective changes were as follows: on the 100-W step, −1.19 ± 0.63 μg · dL^{-1} with H and −2.47 ± 1.10 with N; on the 150-W step, −2.86 ± 0.94 with H and −3.49 ± 0.96 with N; and on volitional exhaustion, −1.66 ± 0.66 with H and −3.41 ± 0.83 with N. For LA, the changes amounted to +2.07 ± 0.27 mmol · L^{-1} with H and +1.03 ± 0.21 with N on the 100-W step ($P < .001$). On the 150-W step, they were +5.20 ± 0.58 mmol · L^{-1} with H and +3.14 ± 0.48 with N ($P < .001$). On volitional exhaustion, they were +8.27 ± 0.39 mmol · L^{-1} with H and +8.00 ± 0.50 with N.

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DISCUSSION

The partial pressure of O_2 in the blood together with the response of LA during exercise indicate that acute hypoxia with increased anaerobic tissue metabolism existed on the H day. The responses of CORT support the notion of increased stress brought about by physical exercise. There was also an increased response of ET to exhaustive exercise in combination with hypoxia. Albeit slight, this modification confirms prior in vitro reports that during hypoxia the excretion of the peptide is augmented. Approximately 80% of the ET production is supposedly released abluminally, with the peptide acting primarily as an autocrine-signaling factor promoting local vasoconstriction, whereas 20% is secreted intravasally. Furthermore, there is a high clearance rate of unbound ET in the lung and in the kidneys. ET concentrations are highest at their site of secretion and thus are locally active. Therefore, it must be assumed that ET measured in a peripheral vein reflects a local spillover.

We conclude that in this study a modified response of ET in man to hypoxia was detected when the additional stress of exhaustive physical labor was applied. However, the physiological relevance of this effect remains to be elucidated in future studies.

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