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BRIEF REPORT

The Effects of Sympathetic Inhibition on Metabolic and Cardiopulmonary Responses to Exercise in Hypoxic Conditions

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Objective.—Pre-exertion skeletal muscle glycogen content is an important physiological determinant of endurance exercise performance: low glycogen stores contribute to premature fatigue. In low-oxygen environments (hypoxia), the important contribution of carbohydrates to endurance performance is further enhanced as glucose and glycogen dependence is increased; however, the insulin sensitivity of healthy adult humans is decreased. In light of this insulin resistance, maintaining skeletal muscle glycogen in hypoxia becomes difficult, and subsequent endurance performance is impaired. Sympathetic inhibition promotes insulin sensitivity in hypoxia but may impair hypoxic exercise performance, in part due to suppression of cardiac output. Accordingly, we tested the hypothesis that hypoxic exercise performance after intravenous glucose feeding in a low-oxygen environment will be attenuated when feeding occurs during sympathetic inhibition.

Methods.—On 2 separate occasions, while breathing a hypoxic gas mixture, 10 healthy men received 1 hour of parenteral carbohydrate infusion (20% glucose solution in saline; 75 g), after which they performed stationary cycle ergometer exercise (~65% maximal oxygen uptake) until exhaustion. Forty-eight hours before 1 visit, chosen randomly, sympathetic inhibition via transdermal clonidine (0.2 mg/d) was initiated.

Results.—The mean time to exhaustion after glucose feeding both with and without sympathetic inhibition was not different (22.7 ± 5.4 minutes vs 23.5 ± 5.1 minutes; $P = .73$).

Conclusions.—Sympathetic inhibition protects against hypoxia-mediated insulin resistance without influencing subsequent hypoxic endurance performance.

Key words: sympathetic nervous system, insulin sensitivity, muscle glycogen

Introduction

Pre-exertion skeletal muscle glycogen content is a determinant of endurance exercise performance[1]; low glycogen stores contribute to premature fatigue, whereas high glycogen promotes and extends performance. In low-oxygen environments, the contribution of carbohydrates to endurance performance is further enhanced as glucose and glycogen dependence is increased. In hypoxia or hypobaria, insulin sensitivity is decreased markedly in healthy adult humans.[2–4] In light of this insulin resistance, maintaining skeletal muscle glycogen in high altitudes becomes difficult; thus, subsequent endurance performance is impaired. Low-oxygen–mediated activation of the sympathetic nervous system may contribute to high-altitude insulin resistance, in part via glycogenolysis, lipolysis, and inhibition of hexokinase and insulin receptor substrate-1–associated phosphatidylinositol 3-kinase. We have demonstrated that sympathetic inhibition with the centrally acting α_2-adrenergic receptor agonist, clonidine, attenuates hypoxia-mediated insulin resistance.[4] This implies that sympathetic inhibition may be an effective strategy to abrogate high-altitude insulin resistance and thus promote skeletal muscle glycogen maintenance and

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endurance performance in low oxygen. However, the sympathetic nervous system is also a powerful regulator of cardiopulmonary function, and sympathetic inhibition in hypoxia may actually impair endurance exercise performance via decreased cardiac output and oxygen delivery. The purpose of the current investigation was to examine the hypothesis that the metabolic benefits of sympathetic inhibition outweigh the cardiopulmonary decrement as they pertain to endurance exercise performance in hypoxia after carbohydrate feeding.

Methods

Ten men participated in this study. Inclusion criteria included age within the range of 18 to 40 years and body mass index ranging from 18.5 to 30 kg/m^2; freedom from overt disease based on medical history, assessment of blood pressure, and 12-lead electrocardiogram at rest and during incremental exercise; and physician approval. Exclusion criteria included current use of tobacco or medications, history of acute mountain sickness, pulmonary dysfunction, and contraindications to vigorous exercise, as per the American College of Sports Medicine. The institutional review board at Colorado State University approved the protocol. The purpose and risks of the study were explained to research participants before written informed consent was obtained.

OVERVIEW

After screening, participants reported to the laboratory on 2 separate occasions; 48 hours before 1 of these visits, transdermal administration of clonidine was initiated. The study visits occurred in random order and began with 1 hour of parenteral carbohydrate feeding, after which participants performed moderate-intensity cycle ergometer exercise until exhaustion. Throughout the entirety of each visit, including the exercise component, participants breathed a hypoxic gas mixture.

SCREENING AND HABITUATION

Body composition (dual-energy x-ray absorptiometry; Lunar Radiation Corp, Madison, WI; software v. 4.1) and maximal oxygen uptake (V_{O_2}max; indirect calorimetry, Parvo Medics, Sandy, UT) were assessed, as previously described.[5] For habituation purposes, during a separate visit participants performed cycle ergometer exercise (Velotron; Racermate Inc, Seattle, WA), while breathing hypoxic gas, at an external work rate designed to evoke a metabolic rate equivalent to 65% of V_{O_2}max, determined in normoxia. Exercise intensity was verified via indirect calorimetry. Participants cycled until they were unable to maintain a pedal cadence greater than 40 rpm.

EXPERIMENTAL PROCEDURES

After screening and protocol habituation, participants reported to the laboratory on 2 separate occasions, after an overnight fast and 48-hour abstention from vigorous physical activity. On arrival, participants were instrumented for measurement of heart rate (3-lead electrocardiogram), blood pressure, and oxyhemoglobin saturation (Cardiocap 5, GE Datex-Ohmeda, Madison, WI). Heart rate and systolic blood pressure were used to calculate the rate pressure product. After a brief period of semirecumbent rest, heart rate, blood pressure, and oxyhemoglobin saturation were recorded. Participants were then fitted with a face mask (7450 Series; Hans Rudolph, Inc, Shawnee, KS) attached to a 3-way, nonrebreathing valve (2730 Series; Hans Rudolph, Inc) and connected to a 100-L nondiffusing gas bag (6000 Series; Hans Rudolph, Inc) filled with precision mixed gases (15% O_2, balance N; Airgas, Denver, CO). After 15 minutes, heart rate, blood pressure, and oxyhemoglobin saturation were recorded again. Glucose (20% glucose solution in saline; 75 g) was intravenously administered for 1 hour, after which the participants rested quietly for 3 hours before the time-to-exhaustion trial. Consistent with the habituation protocol, this entailed stationary cycle ergometer exercise at 65% of normoxic V_{O_2}max. Time to exhaustion was recorded as the time at which a pedal cadence of greater than 40 rpm could no longer be maintained. Rating of perceived exertion was recorded.

To determine the influence of sympathetic inhibition on exercise performance in hypoxia after parenteral carbohydrate feeding, during the 48 hours before 1 of the visits, transdermal clonidine (Catapres-TTS; 0.2 mg/d) was administered. Clonidine administration continued until initiation of the glucose infusion. Clonidine is an antihypertensive; the mechanism of action is via prejunctional α_2-adrenergic receptor stimulation. Short-term clonidine use results in centrally mediated peripheral sympathetic inhibition, as reflected by attenuated skeletal muscle–sympathetic nerve activity,[6] decreased norepinephrine release,[4,6] and increased heart rate variability. The plasma half-life of clonidine is 21 hours; therapeutic plasma concentrations are usually achieved within 48 hours of initiation of transdermal administration.[7]

STATISTICAL ANALYSIS

One-way repeated measures analysis of variance was used to determine the influence of sympathetic inhibition on exercise time to exhaustion after carbohydrate feeding. Statistical significance was set at $P < .05$. Data are expressed as mean ± SE.