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Effect of hypoxia on cerebrovascular and cognitive function during moderate intensity exercise☆

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HIGHLIGHTS

- The effect of hypoxia on cerebrovascular hemodynamics and cognition was tested.
- Accuracy was maintained while reaction time increased during hypoxic exercise.
- Hypoxic exercise decreased prefrontal oxygenation despite increased cerebral flow.
- Slowed reaction time during hypoxic exercise may be due to behavioral strategies.

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ABSTRACT

Exercise in hypoxia places added demands on the brain and cerebrovasculature that can impact cognitive function. The purpose of this study was to investigate the effect of acute hypoxia on cerebrovascular hemodynamics, markers of neuro-steroidal modulation and brain-blood barrier (BBB) integrity, and cognition during exercise. Thirty healthy participants (21 ± 4 yrs., BMI 24.0 ± 2.6 kg·m^{-2}; 15 men) were randomized to both a ≈ 2.5 h normoxic (FiO_2 20.0%) and hypoxic (FiO_2 12.5%) condition on two separate days. After 1.25 h, participants underwent 10 min of exercise-alone (cycling at 55% HRmax) and 15 min of exercise + cognitive testing. Prefrontal cortex (PFC) tissue oxygenation and middle cerebral artery (MCA) mean blood velocity (MnV) were measured using near-infrared spectroscopy and transcranial Doppler respectively at rest, during exercise-alone, and during exercise + cognitive testing. Salivary levels of dehydroepiandosterone [DHEA], DHEA-sulfate [DHEAS]) and neuron specific enolase (NSE) were measured pre and post exercise. Cognition was assessed using standard metrics of accuracy and reaction time (RT), and advanced metrics from drift-diffusion modeling across memory recognition, N-Back and Flanker tasks. MCA MnV increased from rest to exercise ($p < 0.01$) and was unchanged with addition of cognitive testing during exercise in both normoxia and hypoxia. PFC oxygenation increased during exercise ($p < 0.05$) and was further increased with addition of cognitive challenge in normoxia but decreased during exercise in hypoxia ($p < 0.05$) with further reductions occurring with addition of cognitive tasks ($p < 0.05$). DHEA and NSE increased and decreased post-exercise, respectively, in both normoxia and hypoxia ($p < 0.01$). Accuracy on cognitive tasks was similar in normoxia compared to hypoxia, while RT was slower in hypoxia vs normoxia across memory recognition ($p < 0.01$) and Flanker tasks ($p = 0.04$). Drift-diffusion modeling suggested changes in memory RT were due to increases in caution ($p < 0.01$). Overall cognitive performance is maintained during exercise in hypoxia concomitant with slower RT in select cognitive tasks and reduced oxygenation in the PFC. These changes were accompanied by slight increases in neuro-steroidal modulation but appear independent of changes in NSE, a biomarker of BBB integrity. Maintained accuracy and select increases in RT during hypoxic exercise may be related behavioral changes in caution.

1. Introduction

Cognitive function relies on adequate oxygen delivery to the brain via the cerebrovasculature. As brain activity increases, blood flow must increase to meet neural/metabolic demands [1], a process known as neurovascular coupling (NVC) [2–4]. NVC has been shown

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to be a significant determinant of cognitive performance [5,6]. Given the importance of oxygen for optimal NVC, disturbances such as hypoxia pose a significant threat to cognitive performance. Indeed, acute hypoxic exposure reduces cognitive function in several domains such as memory and executive functions [7–11]. Additionally, low-intensity exercise in hypoxia decreases cerebral oxygenation [12,13]. Thus, exercise compounds the challenge to arterial oxygen saturation and cerebral oxygenation in hypoxia, potentially impacting cognitive performance even further [14]. Understanding the impact of hypoxia on NVC and cognitive performance at rest and during exercise has important implications for individuals subject to hypoxic duress as a result of exposure to high altitude environments (i.e. military personnel); a challenge likely made worse by concomitant physical exertion.

Optimal NVC is highly dependent on integrity of the neurovascular unit. The neurovascular unit is comprised of cerebrovasculature (endothelium and smooth muscle), the brain-blood-barrier (BBB), neurons, and non-neuronal cells. The BBB serves to regulate axonal and synaptic extracellular environments, acting as a physical, metabolic, transport, and immunologic barrier [15]. Due to its critical role in brain function, any BBB disruption could impair neural function and thus cognitive function [16]. Hypoxic exposure may increase oxidative stress, causing transient BBB disruption [17–19] and associated vascular dysfunction. Neuron specific enolase (NSE) is an enzyme localized in the cytoplasm of neurons [20] and is released systemically with BBB disruption. NSE is sensitive to oxygen tension and has been linked to cognitive performance in select clinical populations [21]. As such, measuring NSE following exercise in hypoxia may provide insight into potential compromises in BBB integrity in this setting. Conversely, aerobic exercise itself may protect and improve BBB integrity through its effects on neuro-steroids dehydroepiandrosterone (DHEA) and its sulfated counterpart (DHEA-S). DHEA/S, which can be synthesized by the brain (see ref. [22,23] for review), increase following moderate-intensity aerobic exercise [24] and short-duration (5 min) hypoxic challenges [25], and appear to play a role in neuroprotection and preservation of BBB permeability [23,26,27]. As such, DHEA/S has been shown to have a favorable effect on cognitive function (memory, executive function, and attention [28]). The effect of exercise in hypoxia on NSE and DHEA/S and their relation to NVC and cognitive function has yet to be investigated.

Cognitive function in hypoxia is typically interrogated using measures of either accuracy [7,29], reaction time (RT) [14,30], or both [9,31]. Unfortunately, this can lead to mixed conclusions when slower RT indicates a processing deficit [30], while preservation of accuracy may suggest the contrary [9]. Drift-diffusion modeling (DDM) is a descriptive mathematical approach that decomposes observational data (hits, misses, RTs) into latent processes [32–34]. DDM utilizes all available behavioral data (accuracy, correct/error RTs, shape of correct/error RT distributions) to provide insight into whether changes in cognition are due to neurological (i.e. encoding, motor response) or behavioral (i.e. caution, response bias) changes in the underlying decision-making process. No prior literature has investigated the effects of exercise or hypoxia on cognition using mathematical modeling.

Therefore, the purpose of this study was to investigate the effect of acute hypoxia on cerebrovascular hemodynamics (middle cerebral artery blood velocity and prefrontal cortex tissue oxygenation/deoxygenation), markers of BBB integrity (neuron specific enolase), neurosteroidal modulation (DHEA and DHEA-S), and cognitive function (via DDM) during exercise. It was hypothesized that hypoxia would reduce cerebral oxygenation, increase NSE, attenuate increases in DHEA/S and ultimately impair cognitive function during exercise.

2. Materials and methods

2.1. Participants

Thirty recreationally active men (22 ± 4 yrs., body mass index [BMI] 25.3 ± 3.0 kg·m^{-2}, body fat 11.2 ± 4.8%, hemoglobin 15.0 ± 0.9 g/dL; $n = 15$) and women (20 ± 3 yrs., BMI 22.6 ± 1.2 kg·m^{-2}, body fat 16.7 ± 5.9%, hemoglobin 12.9 ± 1.0 g/dL; $n = 15$) in overall good health were recruited from the local University community for this study. Exclusion criteria included self-reported (determined from a health history questionnaire) smoking, hypertension, diabetes mellitus, hyperlipidemia, pulmonary disease, renal disease, neurological disease, or peripheral artery disease. Hemoglobin concentration was assessed at baseline via finger-stick blood sample and microcuvette (The Hemocue Hemoglobin System, Hb201+; Angelholm, Sweden) to screen for anemia (defined as Hb < 13.5 g/dL and 12.0 g/dL for males and females, respectively). All women were tested during the early follicular phase of the menstrual cycle (days 2–7 when estrogen is at its lowest) to minimize the confounding effects of estrogen on vascular function. Women on oral contraceptives ($n = 9$) were tested during the placebo phase. Otherwise, participants were not taking any medications at the time of the study and were asked to refrain from dietary supplement use for the duration of the study. This study was approved by the Syracuse University Institutional Review Board and all participants provided written informed consent prior to participation.

2.2. Design

Height and weight was assessed via stadiometer and electronic scale, respectively, and body composition was estimated via air displacement plethysmography (BodPod; COSMED, Concord, CA). Prior to the experimental visits, all participants were familiarized with the cognitive tasks and performed a brief semi-recumbent cycling bout to estimate the desired workload for the normoxic exercise trial. Testing was conducted at the same time of day in a temperature-controlled laboratory with experimental trials separated by at least 24 h. Participants were instructed to fast for ≥4 h and avoid vigorous exercise and avoid consuming caffeine and alcohol the day of testing.

Participants underwent exercise and cognitive testing following a ≈ 2-h exposure period in a normobaric hypoxic chamber (K2–1000, Hypoxico Systems, New York, NY) that was set to either a) normoxia (FiO_2, 20.5 ± 0.3; ≈195 m), or b) hypoxia (FiO_2 12.5 ± 0.1; ≈4100 m), in this randomized, crossover design study (Fig. 1). Oxygen concentration was measured continuously using an external oxygen analysis system (TrueOne 2400, ParvoMedics, Sandy, UT). Our hypoxic stimulus (equivalent to approximately 4100 m) was chosen based on previous research that established 4000–5000 m as the critical altitude for changes in cognitive function [35]. Participants underwent 115 min of exposure prior to baseline measures and exercise/cognitive testing.

2.3. Exercise testing

Prior to the start of exercise, participants rested for 10 min in an upright seated position on the semi-recumbent cycle ergometer. Following baseline measures, participants completed a 25 min exercise bout which included 10 min of cycling prior to beginning a 15 min cognitive testing battery. Participants' workloads were individually manipulated to maintain a heart rate response of approximately 50–60% of age-predicted heart rate maximum in both test conditions independently (normoxia and hypoxia). If participants' heart rates strayed substantially from the target heart rate range, the workload was manipulated by changing the resistance or instructing the participant to change cycling cadence. Any changes in workload required during cognitive tasks were only manipulated by adjusting the resistance in order to avoid disrupting participants' concentration during the cognitive task. Any verbal instructions to change cadence were only given between tasks when participants were not actively engaged. The exercise intensity was chosen in order to simulate the relatively low intensity, steady-state exercise often experienced by military and mountain rescue teams in the field. Semi-recumbent cycling was chosen in order to optimize participant comfort during cognitive testing and to reduce movement interference stemming from upright cycle ergometry or