A Metabolic Intervention for Improving Human Cognitive Performance During Hypoxia

Kody Coleman; Jeff Phillips; Michelle Sciarini; Brianna Stubbs; Olivia Jackson; Dawn Kernagis

BACKGROUND: During hypoxia an operator's cognitive performance may decline. This decline is linked to altered brain metabolism, resulting in decreased adenosine triphosphate (ATP) production. Ketone bodies are an alternative substrate to glucose for brain metabolic requirements; previous studies have shown that the presence of elevated ketone bodies in the blood maintains brain ATP levels and reduces cerebral glycolysis during hypoxia. Thus, ketones may be a strategy to mitigate cognitive decline in hypoxia. Ketone ester (KE) consumption allows rapid elevation of blood ketone levels; therefore, we investigated the effects of consuming a KE drink on cognitive performance during hypoxia. Here, we report results of a pilot study.

METHODS: There were 11 subjects who completed a cognitive performance test battery under conditions of normoxia and hypoxia following consumption of a KE drink and a placebo control drink.

RESULTS: Significant hypoxia effects (O_2 saturation minimum was found to range between 63% and 88% in subjects) were found for blink duration ($P\eta 2 = 0.665$) and blink rate ($P\eta 2 = 0.626$), indicating that the hypoxia condition was associated with longer blink durations and lower blink rates. Significant hypoxia effects were likewise observed for a code substitution task ($P\eta 2 = 0.487$), indicating that performance on the task was significantly disrupted by the hypoxia stressor. KE consumption had a significant effect on blink duration ($P\eta 2 = 0.270$) and the code substitution task ($P\eta 2 = 0.309$).

DISCUSSION: These finding suggest that some effects of acute hypoxia can be mitigated by nutritional ketosis.

KEYWORDS: ketones, altitude, cognitive performance, hypoxia.

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Special Operations forces often conduct extended, high-altitude missions which demand intense physical and cognitive exertion. As altitude increases, atmospheric pressure falls, leading to a lower oxygen partial pressure in inspired air. Diffusion of oxygen into the blood is reduced and its resulting delivery to tissues of the body is consequently compromised. Hypoxia-induced degradation of both individual and group performance during high altitude exposure has been documented in previous controlled studies.[1,16,21] Therefore, there is an urgent need for solutions that can sustain or augment operator performance during missions and maximize the efficiency of training and acclimation exposures.

Brain Metabolism During Hypoxia

The brain has a high oxygen requirement (127 ± 7 mmol/100 g/min)[11] and thus is particularly sensitive to hypoxia. During hypoxia, brain energy metabolism is altered, with an increase in anaerobic energy production and lactate accumulation.[12,21,30] This metabolic shift is likely to contribute to the deterioration of operational function found in previous research. Therefore, countermeasures that address this metabolic shift may be key to mitigating the impact hypoxia has on operator performance. One such countermeasure is nutritional ketosis.[13,22,30]

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Ketosis

Ketosis refers to the presence of elevated ketone bodies in the blood (> 0.5 mmol · L^{-1} beta-hydroxybutyrate; BHB). In human physiology, 'ketone bodies' refers to the metabolites BHB, acetoacetate, and acetone; these small molecules are produced naturally in the liver using lipids as a result of carbohydrate restriction.

Crucially, ketone bodies act as an alternative substrate to sustain cerebral metabolism when glucose is limited, accounting for up to 80% of brain energy metabolism in conditions of prolonged starvation.[19] Glucose stores are relatively small, representing enough energy to maintain brain function for 24–48 h. The energy reservoir represented by stored lipids is vast; however, fat cannot be oxidized in sufficient quantities to sustain brain function.[25] Conversion of fat into ketones is a way to make this pool of energy accessible to the brain, as ketone bodies can readily cross the blood-brain barrier.

Beyond their role as a metabolic substrate, there are further advantages offered by ketone metabolism in the brain and other organs. First, the mitochondrial oxidation of ketones is energetically advantageous, increasing the efficiency of an isolated perfused heart by 24% compared to the metabolism of glucose alone.[24] Secondly, ketones can protect mitochondrial function as they can act as scavengers of potentially harmful reactive oxygen species.[9] Furthermore, ketones are endogenous inhibitors of histone deacetylase enzymes[26] and can thus modulate gene expression. Downstream effects of histone deacetylase inhibition are diverse, but one pertinent effect is an upregulation in the expression of brain-derived neurotrophic factor[28] (a neuron protective factor molecule). Finally, ketones may have a clinically relevant systemic and neurological anti-inflammatory effect through inhibition of the NLRP3 inflammasome.[30,31] These combined effects make ketones an attractive, natural strategy to sustain and protect the body and brain.

Nutritional Ketosis

Nutritional (diet-induced) ketosis is typically induced by fasting or by following a ketogenic diet (very low carbohydrate, low-moderate protein, high fat macronutrient ratio). The time taken to reach a state of ketosis depends on many factors (i.e., habitual diet, exercise status). Generally, ketone levels exceed 0.5 mmol · L^{-1} after 24−48 h of fasting and can take up to 10 d to reach a physiological plateau at 6–8 mmol · L^{-1}.[3,15] During a ketogenic diet, blood ketone levels are dependent on adherence and time on the diet, with reported values ranging from 0.8 mmol · L^{-1} up to 4 mmol · L^{-1}.[6,8]

However, use of the ketogenic diet or fasting to achieve ketosis is widely considered to be impractical in operational settings due to difficulty in sustainability and unwanted side effects, such as cramping or even impaired mitochondrial efficiency and cognitive function.[6] Therefore, alternative approaches are required to deliver some of the benefits of ketone metabolism rapidly and without the requirement for fasting or a restrictive ketogenic diet.

Exogenous Ketosis and Ketone Esters

In contrast to the slow process of inducing ketosis through fasting or a ketogenic diet, consumption of a ketone ester (KE) such as R,1-3 beta-hydroxybutyrate R,1-3 butanediol can deliver rapid (<30 min) and sustained (~4 h) ketosis in a predictable, dose-dependent manner.[4,27,29] This KE has undergone extensive safety testing to demonstrate its generally recognized as safe status as recognized by the U.S. Food & Drug Administration and has been studied in healthy adults at rest,[4,27,29] during and after exercise,[5,7,10] and in several clinical case studies.[2,18] The KE undergoes hydrolysis in the gut to form BHB and butanediol, the latter undergoes hepatic conversion to BHB, and, thus, elevates BHB without the fat, salt, or acid load accompanying other consumable ketone sources. Ketone levels can be elevated >4 mmol · L^{-1} without depletion of carbohydrate stores, even in the presence of a carbohydrate rich meal.[29]

Ketosis, Performance, and Hypoxia

Previous work has demonstrated that exogenous sources of ketones can enhance aspects of cognitive function in rodents,[16] in athletes following intermittent exercise,[7] and can protect against cognitive decline during hypoglycemia in human adults.[20] Animal and in-vitro models of hypoxia strongly suggest a protective effect of the state of ketosis achieved both through diet and exogenously. This was first observed during studies in the 1980s, when artificially raising blood BHB with butanediol (either injected or given orally) increased survival time of mice exposed to hypoxia.[12] Follow up in-vitro work using rodent brain slices confirmed that ketone oxidation increased relative to glucose during hypoxia.[14] Subsequent work has expanded on the mechanisms responsible: infusion of exogenous ketones prior to induction of cerebral hypoxic ischemia allowed maintenance of adenosine triphosphate levels and decreased lactate levels and cerebral water accumulation in rodents.[30] The effect is conserved with both exogenous and endogenous ketones; feeding a ketogenic diet prior to exposure decreased brain lactate accumulation in hypoxia.[21] A particularly compelling study demonstrated that the biological effects of ketosis translated into meaningful behavioral improvements, with both ketogenic diet and ketone infusions attenuating the spatial memory impairment caused by hypobaric hypoxia in rodents.[31] Despite these promising basic science results, prior to this project, no research to date had addressed whether ketosis can improve cognitive function in humans exposed to hypoxia. We addressed this gap by conducting the following experiment.

METHODS

Subjects

A randomized, single-blind (subjects were blinded to the study drink), placebo-controlled, cross-over study was conducted to assess the effect of a KE drink on cognitive performance under conditions of normobaric hypoxia. The study protocol was reviewed and approved by the IHMC Institutional Review Board and SOCOM Human Research Protection Office prior to study commencement. The study was preregistered at clinicaltrials.gov (NCT03659825). Written informed consent was obtained from each individual prior to participation; subjects also completed a medical questionnaire to confirm eligibility ahead of the study visits.

For this study, using a sample size calculator based on a priori knowledge of the cognitive task battery and the KE drink, we estimated that we required 16 subjects to complete all conditions. Recruited were 19 military aviation students stationed at Marine Aviation Training Support Group 21 (MATSG-21) at NAS Pensacola with Command approval. A total of 11 subjects (N = 11) completed the baseline visit and the two study days. There were 3 subjects who completed the baseline visit and Study Day 1, but, due to Command training schedule or promotions, were unable to schedule Study Day 2. The remaining subjects were unable to schedule Study Day 1 and 2 due to Command training schedule or promotion. Subjects were healthy men, ages 23–26 yr (mean age = 24.3 ± 1.2 yr), with physical and cognitive baseline measures that were similar to the Special Operations forces population. The weight range for the 11 subjects was 74.7–114.9 kg; mean weight = 85.2 ± 11.1 kg (164.6–253.4 lb; mean weight = 187.8 ± 24.5 lb). For this initial assessment, given the potential differential effect of the female hormonal cycle on cognitive performance, no women were included in this study. In addition, no efforts were made to recruit individuals of a specific ethnic background.

Materials

During each test visit, subjects consumed two study drinks containing a bodyweight-adjusted amount of KE or a volume and taste-matched placebo drink. The KE was supplied by HVMN Inc, San Francisco, CA, USA. The order of study drink administration was randomized. For the KE condition, the initial study drink contained 400 mg $\cdot$ kg^{-1} of the 'active' ketone ester, and the second 'top-off' study drink contained 150 mg $\cdot$ kg^{-1} of KE to maintain blood ketone levels and maintain a steady state throughout the experiment. The placebo drinks were made using the same flavor mix used in the KE drink (HVMN Inc), with a vanishing amount of a bitter flavor (Bitrex, Edinburgh, Scotland) added to mimic the taste of the KE.

Given that functional impairments are thought to accumulate predictably and repeatedly at decreasing oxygen levels,[31] lab-induced hypoxia is a relevant and straightforward model of the extreme environment experienced by operators. Here, we used a reduced oxygen breathing device (ROBD) to experimentally induce hypoxia.[3,4]

The cognitive tests were administered using a hand-held tablet computer that contains the DANA software (Anthrotronix, Silver Spring, MD, USA) and an eye-tracking device (RightEye, Bethesda, MD, USA). The DANA and RightEye software contain various cognitive tests. For this study, we used the Simple Reaction Time test, the Procedural Reaction Time test, and the Code Substitution-Simultaneous test with DANA. We used the Simple Reaction Time test, a Choice Reaction Time test, and a Discriminate Reaction Time test with RightEye. Furthermore, measures of neurological status, including blink duration and blink rate, were measured with RightEye.

Procedures

The study involved three separate visits to the IHMC (Pensacola, FL, USA): a baseline visit to familiarize subjects with the study procedures and tests, and two test visits. Subjects were randomized to either receive the placebo control drink on the first test visit and KE on the second test visit (condition A), or KE on the first test visit and placebo control drink on the second test visit (condition B) (**Fig. 1**). Cognitive performance in both normoxia and hypoxia were assessed in each condition.

Subjects were asked to avoid alcohol and caffeine for at least 12 h prior to the study, to refrain from eating 7 h prior to study arrival, to consume a similar meal the evening prior to study day, and to maintain their normal sleep and hydration routine prior to each visit. The baseline visit consisted of medical review, consent, and familiarization with the study equipment and cognitive testing. During this visit subjects completed one cognitive session while wearing the ROBD facemask.

Study visit start times were the same for both test days for each participant. There was a minimum 48-h washout between each study visit. At the start of each study visit, subjects completed a compliance questionnaire (to confirm standard sleep, alcohol, caffeine use). A urine sample was obtained to measure specific gravity with a refractometer pen (ATAGO, Bellevue, WA, USA) as an indicator of hydration status. Following urinalysis, subjects consumed a standard meal that consisted of a bagel and the choice of either peanut butter or cream cheese. Subjects were allotted unlimited water bottles, the volume of which was recorded at the end of each day. A baseline cognitive assessment was completed without the ROBD mask once the participant was finished with their meal. After the meal, subjects rested at the test facility for 2 h to allow time for gastric emptying to occur and thus avoid a possible impact of food on the absorption of the study drink. Once the 2 h had elapsed, a baseline capillary blood sample was obtained and then the first study drink was consumed.

Throughout the study visit, capillary blood samples were obtained from a finger using a lancet and immediately analyzed for glucose and ketone levels using a handheld meter (Precision Extra, Abbott, Chicago, IL, USA) and glucose and ketone test strips (Abbott, USA). These samples were taken at the following time points: 2 h after standard meal (immediately prior to study drink 1), 30 min after study drink 1 (immediately prior to normoxic cognitive battery), following first 'recovery' battery (immediately prior to study drink 2), 30 min after study drink 2 (immediately prior to hypoxic cognitive battery), and following second 'recovery' battery.

The participant donned a continuous-flow oronasal mask attached to a ROBD (Environics, Tolland, CT, USA) 30 min after the first study drink. A supraorbital pulse oximeter electrode (Nellcor, Covidien-Medtronic, Minneapolis, MN, USA) was used to monitor arterial oxygen saturation and heart rate. The normoxic condition was then induced using the ROBD. After 5 min of breathing with the mask, the cognitive test battery commenced, lasting 30 min (details below). The mask was then removed and subjects completed a 'recovery' battery of tests (#3). Subjects then consumed a second study drink (a lesser amount than the first study drink) to maintain KE level and rested 30 min before redonning the ROBD mask

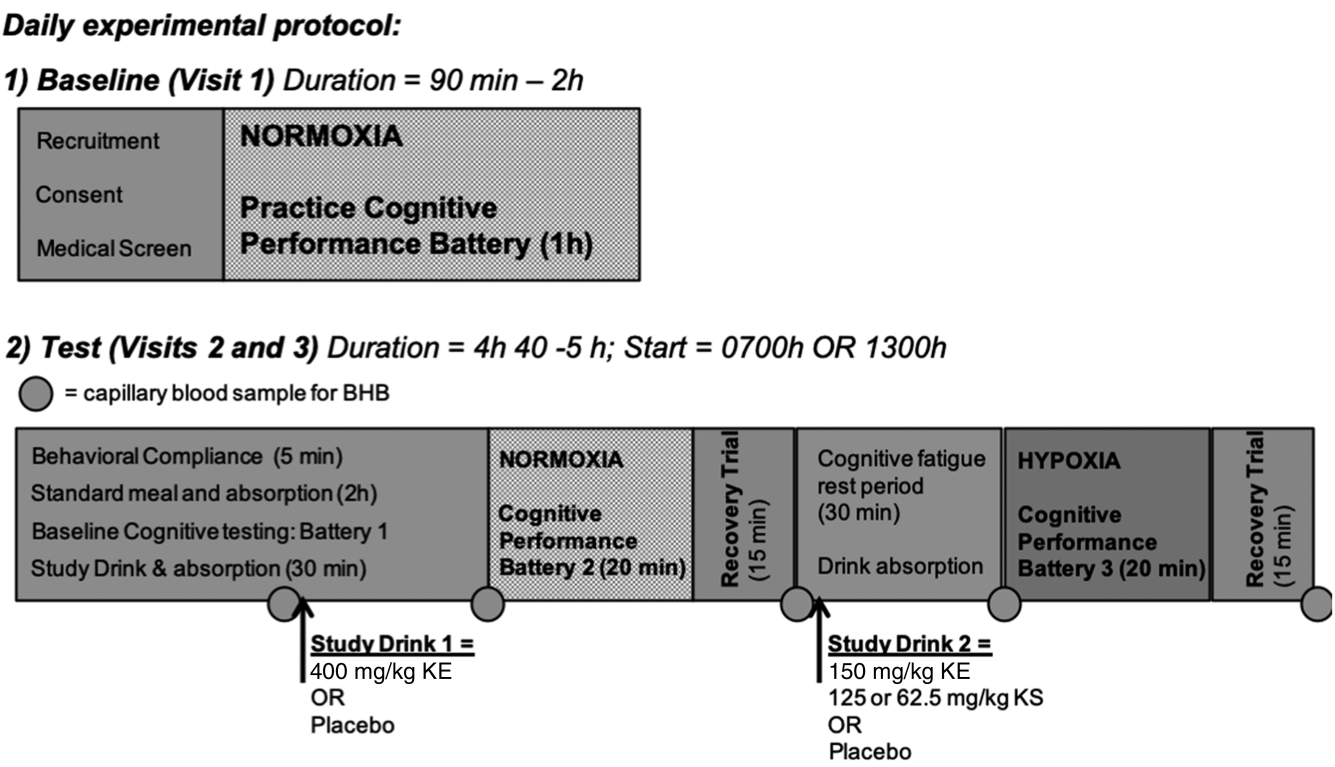

Fig. 1. The study outline and procedures.

and pulse oximeter electrode. The hypoxic condition was then induced by the ROBD at a simulated altitude of 5029.2 m (16,500 ft). Cognitive testing (#4) commenced and lasted 30 min. Once the hypoxic exposure was completed, the mask was removed and subjects again completed the 'recovery' battery (#5).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics Version 25. Data were analyzed for normality and to ensure sphericity assumptions were not violated. Subsequently, appropriate parametric tests with corrections for multiple comparisons were performed. A series of repeated measures ANOVAs were conducted on each dependent variable to determine whether there was significant treatment (ketone vs. placebo), stressor (hypoxia, normoxia), or treatment by stressor interaction effects. Alpha was set at $P < 0.05$ due to the applied nature of this work and the likely decision criterion for the target population.

RESULTS

Following the initial dose, blood ketone levels were significantly higher in the KE condition when compared to placebo [$F(1,10) = 703.297$, $P < 0.01$, $P\eta 2 = 0.986$ (see **Fig. 2**)]. As expected, significant hypoxia effects were observed for blood oxygen saturation [$F(1,10) = 87.055$, $P = 0.00$, $P\eta^2 = 0.897$] and heart rate variability [$F(1,10) = 9.274$, $P = 0.012$, $P\eta^2 = 0.481$], indicating lower blood oxygen saturation and heart rate variability in the hypoxia condition when compared to the normoxia condition. Arterial oxygen saturation minimum in subjects ranged between 63% and 88%.

There were no significant differences in the normoxia condition between KE and placebo among neurological and neurocognitive tests. Significant hypoxia effects were found for blink duration [$F(1,10) = 19.809$, $P = 0.001$, $P\eta 2 = 0.665$] and blink rate [$F(1,10) = 16.715$, $P = 0.002$, $P\eta 2 = 0.665$], indicating that the hypoxia condition was associated with longer blink durations (M = 4.582, SE = 0.534 vs. M = 7.426, SE = 0.583) and lower blink rates (M = 5.285, SE = 0.761 vs. M = 3.532, SE = 0.396). Significant hypoxia effects were likewise observed for the code substitution task [$F(1,10) = 9.481$, $P = 0.012$, $P\eta 2 = 0.487$], indicating that task scores were significantly higher in the normoxia condition (M = 53.47, SE = 2.318) as compared to the hypoxia condition (M = 53.90, SE = 2.554). The most important analyses performed involved treatment by stressor interaction effects as they indicated whether the KE provided protection from the neurological effects of hypoxia. Specific emphasis was placed on metrics that showed a significant degradation in association with hypoxia exposure. Among variables significantly degraded by hypoxia, blink duration was shorter for the KE (M = 6.423, SE = 0.453) than for the placebo condition (M = 8.429, SE = 1.212). Furthermore, code substitution scores were higher in the KE during hypoxia exposure (M = 53.048, SE = 2.234) than in the placebo condition [M = 49.732, SE = 2.983; $F(1,10) = 4.62$, $P = 0.061$, $P\eta 2 = 0.309$ (see **Fig. 3**)]. No further effects of KE administration were seen on other neurocognitive outcomes. Treatment and stressor effects on all neurocognitive results are summarized in **Table I**.

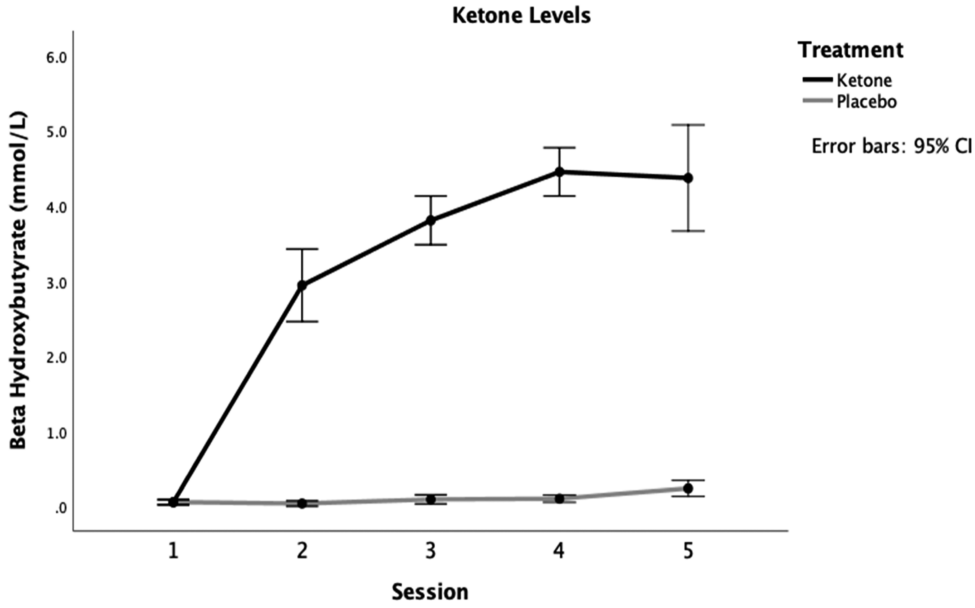

Fig. 2. The average beta hydroxybutyrate level (mmol · L^{-1}) of the subjects at each session. Error bars represent the 95% confidence interval for the data.

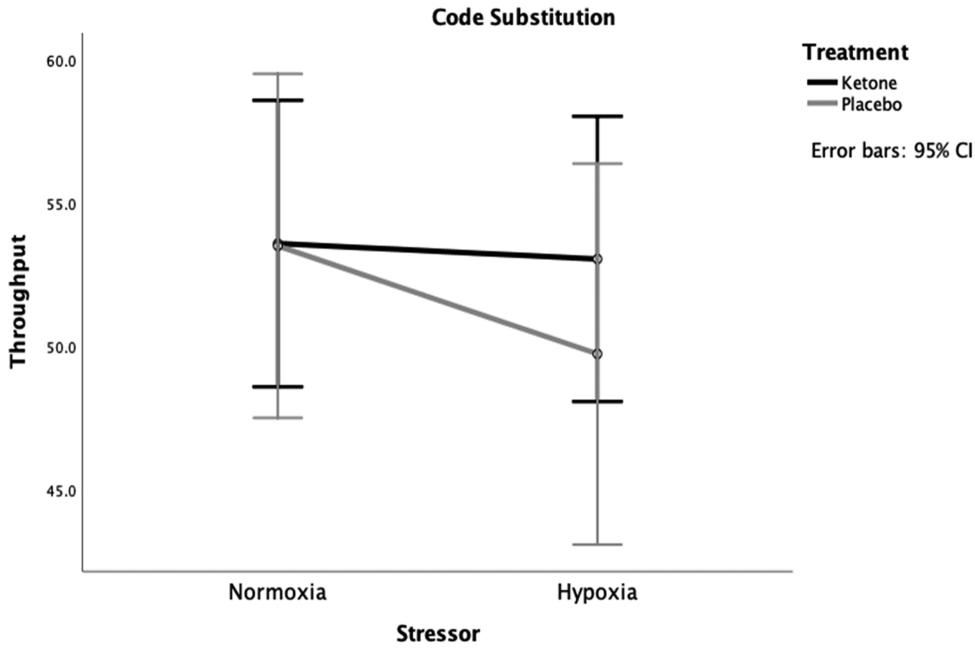

Fig. 3. The throughput scores of the DANA task during both normoxic and hypoxic conditions. Error bars represent the 95% confidence interval for the data.

DISCUSSION

This study demonstrated the efficacy of raising blood ketone concentrations with a ketone ester drink, and a protective effect thereof on neurocognitive measures against the effects of acute, mild hypoxia. Considering both occulometric and cognitive outcomes, there were surprisingly few changes between the normoxia and hypoxia condition. This may have been due to the relatively mild hypoxia used in this experiment (16,500 ft/5029.2 m). The results of the occulometric testing showed that only blink duration and blink rate were significantly affected by hypoxic exposure. An additional consideration is that in our hands the occulometric performance parameters showed low test-retest reliability, which may have further obfuscated any potential hypoxia effects. Low test-retest reliability appeared to be associated with head movements outside of the

Table I. The Statistical Results of the Physiological, Occulometric, and Cognitive Metrics for the Treatment (Ketone vs. Placebo), Condition (Normoxia vs. Hypoxia), and Treatment × Condition Interactions.

Metrics	Treatment			Condition			Treatment × Condition		
Right Eye	***F*-value**	***P*-Value**	***P* Eta Squared**	***F*-Value**	***P*-Value**	***P* Eta Square**	***F*-Value**	***P*-Value**	***P* Eta Square**
Choice Reaction Time-Reaction Time	$F(1,10)=1.548$	0.242	0.134	$F(1,10)=2.140$	0.174	0.176	$F(1,10)=1.103$	0.318	0.099
Choice Reaction Time-Visual Reaction Speed	$F(1,10)=0.105$	0.753	0.01	$F(1,10)=0.102$	0.756	0.01	$F(1,10)=0.439$	0.523	0.042
Simple Reaction Time	$F(1,10)=0.707$	0.42	0.066	$F(1,10)=0.570$	0.468	0.054	$F(1,10)=2.021$	0.186	0.168
Discriminant Reaction Time-Reaction Time	$F(1,10)=0.559$	0.427	0.53	$F(1,10)=0.975$	0.347	0.089	$F(1,10)=0.225$	0.646	0.022
Discriminant Reaction Time- Visual Reaction Speed	$F(1,10)=0.105$	0.753	0.01	$F(1,10)=0$	0.998	0	$F(1,10)=5.223$	0.045	0.343
Blink Duration	$F(1,10)=0.809$	0.39	0.075	$F(1,10)=19.809$	0.001	0.665	$F(1,10)=3.699$	0.083	0.27
Blink Rate	$F(1,10)=3.124$	0.108	0.238	$F(1,10)=16.715$	0.002	0.626	$F(1,10)=0.171$	0.688	0.017
DANA									
Simple Reaction Time	$F(1,10)=0.668$	0.433	0.063	$F(1,10)=0.009$	0.928	0.001	$F(1,10)=9.510$	0.012	0.487
Procedural Reaction Time	$F(1,10)=0.027$	0.873	0.003	$F(1,10)=0.463$	0.512	0.044	$F(1,10)=2.552$	0.141	0.203
Code Substitution Test	$F(1,10)=1.589$	0.236	0.137	$F(1,10)=9.481$	0.012	0.487	$F(1,10)=4.462$	0.061	0.309
HRV/S_pO_2									
HRV	$F(1,10)=0.425$	0.529	0.041	$F(1,10)=16.337$	0.002	0.62	$F(1,10)=1.919$	0.196	0.161
HRV rMSSD	$F(1,10)=0.002$	0.968	0	$F(1,10)=9.274$	0.012	0.481	$F(1,10)=0.560$	0.472	0.053
Blood Oxygen Saturation Minimum	$F(1,10)=6.749$	0.027	0.403	$F(1,10)=87.055$	0	0.897	$F(1,10)=1.1184$	0.302	0.106

device's ideal range. In fact, supporting this assessment, significant variation was observed for the measure of how far the eyes were apart, which should not change.

The results of the cognitive testing showed a similarly inconsistent effect of hypoxia. Observational, simple, and procedural reaction time did not show a significant decline during hypoxia as might have been expected. Alongside the mild hypoxic exposure, we suggest that the simple nature of those tasks and their low demands on higher-order cognitive processes may explain the lack of hypoxia-induced deficit. In support of this, a significant effect of hypoxia was found for the code substitution task, which places demands on higher-order cognitive processes when compared to simple and procedural reaction time tasks.

Considering only the few variables that did exhibit a significant decline during hypoxia, it was notable that the hypoxia-induced decline in code substitution performance and increased blink duration were attenuated by KE consumption compared to the control condition. We speculate that the physiological stress of hypoxia has greatest effects on the more complex cognitive processing, thus these complex variables are more sensitive to interventions such as nutritional ketosis. Similarly, Evans and Egan found that a stressor (intense exercise) had no effect on lower order cognitive processes (reaction time), but did have an effect on high-order processes; furthermore, ketones attenuated this effect. These results suggest that nutritional ketosis following consumption of KE may provide a degree of protection in the presence of a stressor.

Our study did not elucidate an underlying mechanism. Future work should characterize cerebral uptake and oxidation of exogenous ketones in normoxia and hypoxia as well as looking for corresponding changes in glucose metabolism and lactate production. The limitations of the smaller pilot study are also being addressed by our current efforts, wherein we are using a more extreme hypoxia exposure with a larger sample size to determine if the differences presented here become more robust.

Taken together, these results suggest a promising effect of nutritional ketosis from KE drinks on neurocognitive performance in hypoxia. Such strategies should be further researched as a possible hypoxia countermeasure for operators performing missions in high altitude settings.

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