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The effect of moderate versus severe simulated altitude on appetite, gut hormones, energy intake and substrate oxidation in men

Jamie Matu*, Kevin Deighton, Theocharis Ispoglou, Lauren Duckworth

Institute for Sport Physical Activity & Leisure, Leeds Beckett University, Leeds, United Kingdom

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ABSTRACT

Acute exposure to high altitude (>3500 m) is associated with marked changes in appetite regulation and substrate oxidation but the effects of lower altitudes are unclear. This study examined appetite, gut hormone, energy intake and substrate oxidation responses to breakfast ingestion and exercise at simulated moderate and severe altitudes compared with sea-level. Twelve healthy males (mean ± SD; age 30 ± 9years, body mass index 24.4 ± 2.7 $kg \cdot m^{-2}$) completed in a randomised crossover order three, 305 min experimental trials at a simulated altitude of 0 m, 2150 m (~15.8% O_2) and 4300 m (~11.7% O_2) in a normobaric chamber. Participants entered the chamber at 8am following a 12 h fast. A standardised breakfast was consumed inside the chamber at 1 h. One hour after breakfast, participants performed a 60 min treadmill walk at 50% of relative $\dot{V}O_{2max}$. An *ad-libitum* buffet meal was consumed 1.5 h after exercise. Blood samples were collected prior to altitude exposure and at 60, 135, 195, 240 and 285 min. No trial based differences were observed in any appetite related measure before exercise. Post-exercise area under the curve values for acylated ghrelin, pancreatic polypeptide and composite appetite score were lower (all $P < 0.05$) at 4300 m compared with sea-level and 2150 m. There were no differences in glucagon-like peptide-1 between conditions ($P = 0.895$). Mean energy intake was lower at 4300 m (3728 ± 3179 kJ) compared with sea-level (7358 ± 1789 kJ; $P = 0.007$) and 2150 m (7390 ± 1226 kJ; $P = 0.004$). Proportional reliance on carbohydrate as a fuel was higher ($P = 0.01$) before breakfast but lower during ($P = 0.02$) and after exercise ($P = 0.01$) at 4300 m compared with sea-level. This study suggests that altitude-induced anorexia and a subsequent reduction in energy intake occurs after exercise during exposure to severe but not moderate simulated altitude. Acylated ghrelin concentrations may contribute to this effect.

1. Introduction

An increasing number of people ascend to high altitude each year for recreational and occupational purposes and these sojourns often involve rapid ascents that do not allow time for acclimatisation to the hypoxic environment. High altitude exposure can induce a negative energy balance due to appetite inhibition (Bailey et al., 2015; Mekjavic et al., 2016; Wasse, Sunderland, King, Batterham, & Stensel, 2012; Westerterp-Plantenga et al., 1999) and elevated basal metabolic rate (Westerterp, Kayser, Wouters, Le Trong, & Richalet, 1994), in combination with the completion of physically demanding activities such as trekking, skiing and climbing. This may have deleterious effects for performance at high altitude due to a loss of body mass (Rose et al., 1988; Westerterp, Meijer, Rubbens, Robach, & Richalet, 2000; Zaccagni, Barbieri, Cogo, & Gualdi-Russo, 2014), and possibly functional capacity (Hoppeler & Vogt, 2001; Sergi et al., 2010).

Historically, studies have attributed altitude-induced appetite inhibition to acute mountain sickness (AMS). However, it has been found that appetite remains inhibited once the symptoms of AMS have subsided (Tschop & Morrison, 2001). In an attempt to identify possible mechanisms behind altitude-induced anorexia, studies have investigated changes in the circulating levels of various hormones in response to hypoxia. This includes the measurement of glucagon-like peptide-1 (GLP-1) (Mekjavic et al., 2016; Snyder, Carr, Deacon, & Johnson, 2008), leptin (Mekjavic et al., 2016; Sierra-Johnson, Romero-Corral, Somers, & Johnson, 2008), pancreatic polypeptide (PP) (Riepl et al., 2012) and peptide YY (PYY) (Mekjavic

* Corresponding author. Carnegie Research Institute Room 104, Institute for Sport Physical Activity & Leisure, Leeds Beckett University, Leeds, LS6 3QS, United Kingdom.
E-mail address: J.Matu@leedsbeckett.ac.uk (J. Matu).

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et al., 2016; Wasse et al., 2012) with particular recent interest towards acylated ghrelin (Bailey et al., 2015; Morishima & Goto, 2016; Wasse et al., 2012). Wasse et al. (2012) found that a seven hour exposure to hypoxia (12.7% FiO_2, ~4000 m), commencing with a one hour exercise period, significantly reduced acylated ghrelin concentrations and *ad-libitum* energy intake compared with sea-level. However, reports in the literature present contradictory findings regarding the response of acylated ghrelin to moderate altitude (1500 m - 3500 m). In this regard, Bailey et al. (2015) reported lower acylated ghrelin area under the curve (AUC) concentrations in hypoxia (14.5% FiO_2, ~2980 m) than normoxia, whereas Morishima and Goto (2016) found no significant effect of a seven hour moderate hypoxic exposure (15% FiO_2, ~2700 m) on acylated ghrelin concentrations compared with normoxia. The reasons for this discrepancy are unclear and the lack of energy intake assessment in these studies means that the effects of moderate hypoxia on energy intake remains unknown.

In addition to changes in appetite regulation, high altitude exposure also appears to increase the body's reliance on carbohydrate as a fuel for substrate oxidation in comparison with sea-level (Brooks et al., 1991; Katayama, Goto, Ishida, & Ogita, 2010; Peronnet et al., 2006). This response is hypothesised to be acutely beneficial, due to the higher yield of ATP per molecule of oxygen with carbohydrate utilization in comparison with fat (Hochachka et al., 1991). However, this oxygen-efficiency theory has been disputed by other studies which show no effect of altitude on substrate oxidation if relative exercise intensities are matched (Bouissou, Guezennec, Defer, & Pesquies, 1987; Lundby & Van Hall, 2002). An increased reliance on carbohydrate as a fuel could also lead to a faster depletion of valuable and limited liver and muscle glycogen stores (Peronnet et al., 2006), which could have adverse effects at altitude.

Currently the effects of varying severities of normobaric hypoxia on appetite, gut hormones, energy intake or substrate oxidation have not been measured within a single study. Subsequently, this experiment investigated the effect of both moderate (2150 m) and severe (4300 m) simulated altitudes on these variables in comparison with sea-level. The results of this research will help to inform nutritional considerations and practices at both moderate and severe altitude.

2. Methods

2.1. Participants

Twelve healthy male volunteers (age 30 ± 9 years, body mass index 24.4 ± 2.7 $kg \cdot m^{-2}$, body mass 80.5 ± 10.5 kg) provided written informed consent to participate in this study. The study, which received institutional ethics approval, was conducted in accordance with the Declaration of Helsinki. All participants were non-smokers, normotensive, free from food allergies and were not taking any medication. None of the participants had travelled to an altitude >1500 m during the previous three months and were all currently residing at an altitude <500 m.

2.2. Experimental design

Participants were required to make a total of seven visits to the laboratory. The first visit involved screening, anthropometry, verbal familiarisation with testing procedures, a food preferences assessment and a sickle cell trait test. Sickle cell trait was an exclusion criteria due to complications that may occur at altitude, for example splenic infarction (Goodman, Hassell, Irwin, Witkowski, & Nuss, 2014). Further exclusion criteria included diabetes and thyroid disorders.

Over the second, third and fourth visits the participants completed three exercise capacity tests (one at each altitude of 0 m, 2150 m and 4300 m) in order to calculate workloads relative to each altitude for the main experimental trials. These preliminary visits were separated by ≥48 h and conducted in a single-blind randomised fashion using a Latin Square design. Over the fifth, sixth and seventh visits the participants completed three 305 min experimental trials (one at each altitude of 0 m, 2150 m, and 4300 m). These visits were separated by ≥7days and were randomised independently from the maximal exercise tests, also using a single-blind Latin Square design. On the morning of each testing day the following equation was used to calculate and set target FiO_2: *FiO_2 = PiO2 divided by (P_B - 47);* where P_B is barometric pressure in mmHg and 47 mmHg is the vapour pressure of water at 37 °C (Conkin, 2011; Fenn, Rahn, & Otis, 1946). Simulated PiO_2 was 149 mmHg at sea-level (*FiO_2* ~20.9%), 113 mmHg at 2150 m (*FiO_2* ~15.8%) and 83 mmHg at 4300 m (*FiO_2* ~11.7%).

2.3. Exercise capacity tests

Participants completed an exercise capacity test on a treadmill (Woodway PPS 55; Waukesha, WI) which included both a submaximal and maximal phase. The incremental submaximal phase consisted of four, 4 min stages in which the participant walked carrying a 10 kg backpack at a 10% gradient. This exercise modality was chosen to mimic the demands of high altitude activities. The speed of the treadmill was increased by 1 $km \cdot h^{-1}$ each stage and the starting speeds were 3 $km \cdot h^{-1}$, 2 $km \cdot h^{-1}$ and 1 $km \cdot h^{-1}$ for 0 m, 2150 m and 4300 m, respectively. Lower starting speeds were employed in hypoxia based on the knowledge of a reduced aerobic capacity at altitude and the need for all participants to elicit 50% of $\dot{V}O_{2max}$ within the 16 min test. On completion of the submaximal phase participants were allowed 5 min of recovery before commencing the maximal phase. Prior to this phase the participants removed the backpack and the treadmill was set at 1% gradient (Jones & Doust, 1996). The participants then ran at a constant speed, which was dependent upon fitness and altitude, aiming for a rating of perceived exertion (RPE) of 12. The gradient of the treadmill was then increased by 1% per minute until volitional exhaustion. All subjects were deemed to reach $\dot{V}O_{2max}$ as they all expressed >2 of the following criteria: a plateau in $\dot{V}O_2$ in the final exercise stage, respiratory exchange ratio ≥1.15, heart rate within 10 $b \cdot min^{-1}$ of age predicted maximum (220-age), rating of perceived exertion ≥ 19 and/or blood lactate ≥ 8 mM (Howley, Bassett, & Welch, 1995). Expired gas was collected using an online gas analyser (Metalyzer 3B R3; Leipzig, Germany) throughout both phases of this test to allow regression analysis between oxygen consumption and walking speed. This allowed for the calculation of a speed that would elicit 50% of relative $\dot{V}O_{2max}$ whilst walking on a treadmill and carrying a 10 kg backpack at 10% gradient.

2.4. Experimental trials

Participants recorded their food intake for the 24 h prior to the first experimental trial; the quantity and timing of this intake was then repeated before each subsequent trial. Alcohol, caffeine and strenuous exercise were not permitted during this period. Participants consumed a standardised evening meal (1037 kcal, 57% carbohydrate, 28% fat, 15% protein) between 7pm and 8pm on the day before each trial. This meal was consumed to minimise the possibility of a 'second-meal' effect confounding glycemic control or any other measured variables (Stevenson, Williams, Nute, Swaile, & Tsui, 2005; Wolever, Jenkins, Ocana, Rao, & Collier, 1988) and included: fusilli pasta, pasta sauce, cheddar cheese, milk, and jelly