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ORIGINAL CONTRIBUTION

Disturbed eating at high altitude: influence of food preferences, acute mountain sickness and satiation hormones

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Abstract

Purpose Hypoxia has been shown to reduce energy intake and lead to weight loss, but the underlying mechanisms are unclear. The aim was therefore to assess changes in eating after rapid ascent to 4,559 m and to investigate to what extent hypoxia, acute mountain sickness (AMS), food preferences and satiation hormones influence eating behavior.

Methods Participants ($n = 23$) were studied at near sea level (Zurich (ZH), 446 m) and on two days after rapid ascent to Capanna Margherita (MG) at 4,559 m (MG2 and MG4). Changes in appetite, food preferences and energy intake in an ad libitum meal were assessed. Plasma concentrations of cholecystokinin, peptide tyrosine–tyrosine, gastrin, glucagon and amylin were measured. Peripheral oxygen saturation (SpO_2) was monitored, and AMS assessed using the Lake Louis score.

Results Energy intake from the ad libitum meal was reduced on MG2 compared to ZH (643 ± 308 vs. 952 ± 458 kcal, $p = 0.001$), but was similar to ZH on MG4 (890 ± 298 kcal). Energy intake on all test days was correlated with hunger/satiety scores prior to the meal and AMS scores on MG2 but not with SpO_2 on any of the 3 days. Liking for high-fat foods before a meal predicted subsequent energy intake on all days. None of the satiation hormones showed significant differences between the 3 days.

Conclusion Reduced energy intake after rapid ascent to high altitude is associated with AMS severity. This effect

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was not directly associated with hypoxia or changes in gastrointestinal hormones. Other peripheral and central factors appear to reduce food intake at high altitude.

Keywords Hypoxia · Dietary intake · Food preferences · High altitude · Acute mountain sickness

Introduction

Millions of people travel to high or very high altitudes (>2,500 m above sea level) every year enjoying trekking, climbing, skiing or for work, and this has stimulated interest in high-altitude medicine dealing with the effects of hypoxia on human physiology. Nutritional scientists have observed a reduction in energy intake and weight loss in healthy mountaineers in conditions of low oxygen availability [14, 25, 29, 38]. Similar effects have been documented in respiratory disease occurring at sea level. Persistent hypoxia in this patient group is associated with reduced energy intake, weight loss and poor disease outcomes [7]. Moreover, the clinical relevance of hypoxia *independent of disease severity* as a cause of these problems is supported by the finding that oxygen supplementation leads to weight gain in Chronic Obstructive Pulmonary Disease [3].

The partial pressure of oxygen in inspired air falls from about 150 mmHg at sea level to 84 mmHg at 4,559 m (elevation of Capanna Margherita, the highest scientific research station in Europe). At the same time, the incidence of acute mountain sickness (AMS) increases from about 8 % below 4,000 m up to 40 % at 4,559 m [24]. Affected patients complain of gastrointestinal symptoms such as anorexia, nausea and vomiting as well as headache, malaise and trouble sleeping [30]. Despite the association between the two factors, the relative importance of hypoxia *per se* and AMS as a cause of disturbed eating has not been established. Further, the association between energy intake and the severity of AMS is not consistent [25].

Several factors have been proposed to cause reduced eating in hypoxia and AMS. Most refer to central neurological effects such as cerebral edema in AMS [37, 38]; peripheral and gastrointestinal factors, such as alteration in the secretion of neuroendocrine gastrointestinal and pancreatic hormones [1, 11, 20, 32, 41], may however also be important.

Additionally, alterations in food preferences may influence eating behavior at high altitude. Eating is generally controlled by two complementary systems. Homeostatic pathways increase the motivation to eat and restore energy balance in case of depleted energy stores. Hedonic, reward-based mechanisms, however, can override homeostatic controls through cravings or increased desire to eat highly palatable foods [19]. In animal studies, hypoxia decreased the ‘incentive’ to consume food rather than changing ‘hunger’ or ‘appetite,’ thus shifting the taste spectrum toward ‘unpalatable’ for a given diet [8].

The primary aim of this study was to assess changes in food intake and preferences in healthy human subjects after rapid ascent from 446 m to 4,559 m and to assess the roles of hypoxia, AMS and satiation hormones in these changes.

Subjects and methods

Subjects

Thirty-two healthy, experienced mountaineers (20–60 years old) were recruited by posting adverts in alpine journals and by screening the ‘Contact list of rescued people for high altitude disease’ of the last 5 years of the Air Zermatt (Switzerland). This procedure ensured that the study population was enriched by volunteers with experience of or susceptibility to AMS and high-altitude pulmonary edema (HAPE) [22]. Sample size calculation for the entire study was based on the pulmonary outcomes. However, for this substudy, it was estimated that, with a power of 90 % and an α-error of 0.05, a sample size of 21 subjects would be sufficient to detect the differences in food intake between days (sample size calculation based on [25, 38]). Exclusion criteria were more than three nights above 2,500 m in the month preceding study entry; chronic diseases necessitating regular medication such as arterial hypertension, coronary heart disease and pulmonary hypertension; patients with malignancy, transplant patients, patients with clinically significant heart valve disease or with congenital heart or lung disease; lactose intolerance, celiac disease or relevant food allergies or specific food requirements (e.g., vegetarians, Kosher) that could not be provided in the mountain hut. The study was approved by the Ethics Committee of the Canton of Zurich (EK-1677). Written informed consent was received from all subjects.

Study design

This study represents the nutritional science arm of a larger body of work. Other results (e.g., sleep studies, exercise capacity, lung function, lipid metabolism and gastric emptying) will be reported elsewhere. All examinations were carried out at low (Zurich, 446 m above sea level, ZH) and high altitude (Capanna Margherita, 4,559 m above sea level, MG). For the low-altitude examinations, subjects arrived in the late afternoon at the University Hospital Zurich for the sleep studies with other examinations carried out on the following day. For the high-altitude examinations, participants ascended on day 0 by cable car

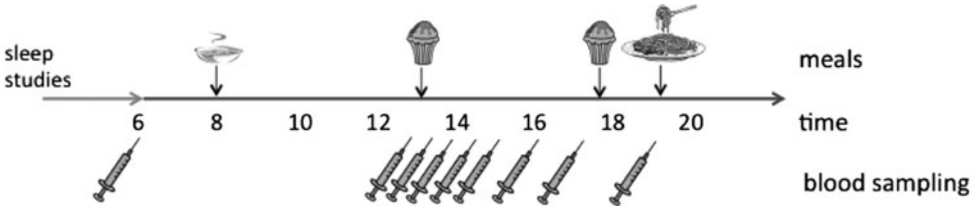

Fig. 1 Schedule of meals and blood sampling for each of the study days (ZH, MG2, MG4)

from Alagna Valsesia (1,200 m, Italy) to about 2,980 m and then hiked to the Rifugio Gniffeti at 3,650 m where they spent one night. On day 1 (MG1), the participants climbed to Capanna Margherita at 4,559 m. Nutritional studies followed on day 2 (MG2) and day 4 (MG4).

All instruments used for the study were tested for functionality at high altitude in a pressure chamber prior to the ascent to Capanna Margherita.

Study protocol

The schedule of meals and other study procedures is presented in Fig. 1. On the morning of each test day, an arterial and a venous catheter were placed in the forearm for blood sampling. Thereafter, unsedated ultra-fine transnasal esophagogastroduodenoscopy was performed to examine the stomach and the duodenum (results to be presented elsewhere). After a standardized breakfast lung function tests, a maximal exercise capacity test on a cycloergometer and echocardiography at rest and during moderate exercise were performed (to be presented elsewhere). Nutritional examinations were all done in the afternoon after the subjects had time to relax. Peripheral oxygen saturation (SpO_2) was monitored by pulse oximetry (finger clip measurement using Infinity by Dräger, Liebefeld, Switzerland) and repetitive arterial blood gas analysis (AVL 5 Radiometer, Copenhagen, Denmark).

Food intake

To control for differences in food intake before the low- and high-altitude examinations, subjects were asked to fill in a weighed food record for 4 days prior to the tests [12]. For each subject, the amount of calories given for breakfast was calculated to meet 30 % of their energy requirements based on medium physical activity [16]. During the day, subjects consumed a fixed energy meal of two muffins (total of 400 kcal; 35 % fat, 10 % protein, 54 % carbohydrates). Four hours later, subjects completed a food preference questionnaire and then consumed again two similar muffins as a preload before an ad libitum dinner 90 min later. For dinner, subjects were offered pasta, bolognese sauce, grated parmesan cheese and two sorts of biscuits. They were free to choose what and how much they ate; all food consumed was weighed to the nearest gram on a kitchen scale by one of the examiners. After dinner, subjects completed a food preference questionnaire as before. After the preload, before and after the dinner, hunger and satiety scores (hunger, desire to eat, amount of food that could be eaten at the moment) as well as gastrointestinal symptoms (feeling of stomach distension and nausea) were assessed on a 100-mm visual analog scale anchored by the statements ‘not at all’ and ‘extremely.’ Unsweetened tea and water were available ad libitum throughout all examination days.

Food preferences

To assess food preferences, a modified hedonic analysis tool was used [9]. Twenty food stimuli were presented to the subjects as color photographs. The food items were assigned to four different categories: high-fat sweet, low-fat sweet, high-fat savory and low-fat savory. Low-fat food was characterized by less than 25 % and high-fat foods by more than 50 % of the energy derived from fat. The different food stimuli used are listed in Table 1.

The assessment of liking (expected liking of each food image category) and relative food preference (non-verbal, motivated choice between food categories) was adapted from Finlayson et al. [9]. For the ‘liking’ measurement, all 20 food items were rated on 100-mm visual analog scales (‘How pleasant would you find the taste of this food at the moment?’). For the assessment of ‘relative preference,’ forced choice methodology was used: Food items from different categories were presented in pairs over a series of

Table 1 Food stimuli used in the food preference questionnaires

High-fat sweet	Low-fat sweet	High-fat savory	Low-fat savory
Milk chocolate	Jelly babies	French fries	Salt sticks
Brownies	Fruit salad	Chips	Bread roll
Cranberry muffin	Marshmallows	Hard cheese	Pasta with tomato sauce
Shortbread	Meringues	Salami	Wild rice mix
Strawberry cream cake	Dried fruits	Salted peanuts	Boiled potatoes

trials and subjects had to choose ‘Which of those foods would you prefer to eat at the moment?’ A total of 60 randomly selected combinations balanced within food categories were used. Food preferences were assessed in a hungry (4 h after fixed energy lunch) and in a satiated state (after ad libitum dinner).

Blood sampling

A total of nine venous blood samples were taken in EDTA tubes for the assessment of gastrointestinal hormones starting with a fasting sample on waking and followed by samples just before the consumption of the muffin lunch as well as 30, 60, 90, 120, 180 and 240 min thereafter until the ad libitum dinner. All blood samples were centrifuged immediately, and the plasma was stored at −80 °C (in freezers at low altitude and in liquid nitrogen at high altitude as well as during transport). Arterial blood for gas analysis was taken during lung function test but not later during the test meal. Before the ad libitum meal, the SpO_2 was measured.

Acute mountain sickness

AMS scores were determined on each test day in the Capanna Margherita based on the Lake Louise scoring (LLS) system with five-rating questions with levels between 0 and 3 (headache, gastrointestinal symptoms, fatigue or weakness, dizziness/light-headedness and difficulty sleeping), and the condition was diagnosed based on the scores as well as repeated clinical examinations. A total score >5 indicated AMS [23, 28].

Medication

Participants who developed severe AMS (Lake Louise score >5) or had a history of high-altitude pulmonary edema (HAPEs) were treated with 2 × 8 mg/day dexamethasone (9-Fluor-16a-methylprednisolone, dexamethasone 4 mg, Galepharm, Küsnacht, Switzerland) starting in the evening of the first examination day (MG2; that is, after the completion of all tests on MG2) until descent. Minor symptoms like moderate headache and nausea were treated with analgesics (Dafalgan®, Paracetamol). Gastrointestinal ulcer and reflux lesions were medicated with Nexium® (Esomeprazole). Diagnosis and prescription of medication were conducted by medical doctors (MM, OG and HF).

Laboratory analysis

Analyses were carried out on plasma samples. Active amylin and glucagon were measured using hormone kits from Millipore Corporation (Milliplex® MAP Human Endocrine Assay, Millipore, Billerica, MA, USA); CCK-8 (active) and PYY 1-36 and PYY 3-36 (truncated form) were measured using radioimmunoassay (RIA) Kits (Eurodiagnostica, Burgdorf, Switzerland) by Prof. Christoph Beglinger, University Hospital Basel; gastrin and EPO were measured using immunoassays (Human Gastrin I (1–17), Enzo Life Sciences, Lausen, Switzerland; Human Erythorpoietin, Quantikine, R&D Systems, Abingdon, UK).

Data analysis

Data were analyzed using SPSS Statistics 17.0 (SPSS, Chicago, IL, USA) and Graph Pad Prism Version 5.0 (San Diego, CA, USA). The Kolmogorov–Smirnov test was used to test the data for normal distribution. Where normal distribution could not be assumed (nausea, feeling of distention), the nonparametric Wilcoxon test was used to test for differences between the different days. For normally distributed data, group comparisons were carried out using *t* tests (unpaired or paired, as appropriate) and one-way ANOVA. For the comparisons of hormone levels between days and time points, two-way ANOVA with post hoc Bonferroni correction was applied. Area under the curve (AUC) was calculated for the hormones using Graph Pad Prism with the concentrations ‘before muffin’ taken as baseline. For food preference data, a general linear model was used with a Bonferroni post hoc test. Multiple linear regression models were carried out to analyze the impact of food preferences on energy intake. Dietary intake data were analyzed using the nutrition software EBISpro for Windows 8.0 (J. Erhardt, University of Hohenheim, Germany) including foods specific to Switzerland.

Results

Of the 32 subjects recruited, three withdrew informed consent before the baseline examination, three withdrew it after the baseline examinations in Zurich and one was excluded due to illness at the baseline examination. Thus, 25 subjects [10 women, 15 men; age 43.8 ± 9.5 years (range 22–60); BMI 23.8 ± 2.2 kg/m^2 (range 20.2–31.4)] completed the study under all conditions. One subject did not finish meals and nutritional questionnaires during the baseline examination, and two subjects were delayed in their ascent the Capanna Margherita due to bad weather and did therefore not participate in the nutritional surveys on MG2 (excluded from analysis). Thus, data of 22 subjects were available for nutritional analysis. Due to a food shortage at the Capanna Margherita during a spell of bad weather and thus no air transport, no cheese was available for the ad libitum meal for seven participants; no macronutrient analysis was conducted for this group.

Table 2 Mean (±SD) Lake Louise Scores (LLS) as well as partial O_2 (PaO_2) and CO_2 ($PaCO_2$) pressure and arterial and peripheral O_2 saturation (SaO_2 and SpO_2, respectively) grouped according to dexamethasone treatment/no treatment ($n = 11$ in each group)

	ZH		MG2		MG4	
	Non treated	Treated	Non treated	Treated	Non treated	Treated
LLS score	0.9 ± 1.0	1.5 ± 1.2[a]	3.4 ± 1.4[b]	5.5 ± 2.3[a,b]	2.3 ± 1.3	1.7 ± 0.9[c]
PaO_2 (kPa)	12.2 ± 1.1	11.9 ± 2.3	5.4 ± 0.6[b]	5.0 ± 0.4[b]	5.8 ± 0.6[b,c]	5.9 ± 0.6[b,c]
$PaCO_2$ (kPa)	5.2 ± 0.4	5.0 ± 0.4	3.8 ± 0.3[b]	3.7 ± 0.3[b]	3.4 ± 0.4[b,c]	3.3 ± 0.3[b,c]
SaO_2 (%)	95.6 ± 0.7	94.1 ± 5.3	77.9 ± 5.4[b]	73.7 ± 6.8[b]	79.1 ± 5.1[b]	80.6 ± 6.0[b,c]
SpO_2 (%)	97.4 ± 1.5	96.9 ± 1.3	78.4 ± 6.0[b]	73.1 ± 9.5[b]	81.6 ± 8.6[b]	79.5 ± 7.7[b]

[a] Significantly different from non-treated group (independent samples *t* test, $p < 0.05$)

[b] Significantly different from ZH

[c] Significantly different from MG2

Hypoxia and AMS

As expected, ascent to 4,559 m caused significant hypoxemia that was partially reversed by acclimatization and/or the intake of dexamethasone at MG4 (Table 2). After the consumption of the preload muffins on MG2, AMS was found in nine participants (39 %). Although patients with the most severe decrease in arterial oxygenation on MG2 tended to have more AMS symptoms and signs, there was no significant correlation between LLS score and oxygen pressure (PaO_2) ($r = 0.15$, $p = 0.494$) and arterial oxygen saturation (SaO_2) ($r = 0.12$, $p = 0.56$).

Effects of dexamethasone on LLS, PaO_2, $PaCO_2$ as well as O_2 saturation are shown in Table 2. While LLS was significantly different between treated and non-treated groups on MG2, none of the other variables were. Following the treatment with dexamethasone, all nine participants recovered from AMS on MG4. Among non-HAPEs, one without AMS at MG2 developed the condition at MG4. A mild HAPE without simultaneous AMS was diagnosed in a HAPEs participant at MG3. This subject was treated with tadalafil (20 mg/day) on MG4 until descent.

Food intake

Based on the analysis of the weighed food records, baseline food intake did not differ at the time just before low- and high-altitude examinations (data not shown).

Mean energy intake (±SD) from the ad libitum dinner on the three examination days was ZH: 952 ± 458 kcal, MG2: 643 ± 308 kcal and MG4: 890 ± 298 kcal. Energy intake was lower on MG2 compared with ZH ($p = 0.001$), but approached the baseline level on MG4 ($p = 0.410$ compared with ZH). The absolute amount of all macronutrients eaten during the ad libitum dinner was reduced on MG2 compared with baseline ($p < 0.05$), but the energy distribution from macronutrients did not change (protein: ZH 19 %, MG2 = 19 %; carbohydrates: ZH = 51 %, MG2 = 53 %; fat: ZH = 30 %, MG2 = 29 %). However, on MG4, the proportion of total energy intake from carbohydrates was reduced (48 %) compared to both ZH and MG2, and that of fat was increased (33 %; $p < 0.05$). Mean energy intake (± SD) at breakfast on all study days was 718 ± 95 kcal, and each subject consumed two times two muffins, which amounted to a total calorie intake of 800 kcal. Thus, the ad libitum dinner contributed 39, 30 and 37 % of total energy intake at ZH, MG2 and MG4, respectively.

Hunger/satiety scores

The hunger/satiety scores are shown in Table 3. The three scores for ‘hunger,’ ‘desire to eat’ and ‘which amount of food could you eat right now?’ given before the meal all correlated positively with the actual energy intake during the meal and on all 3 days (all $p < 0.01$). While the hunger/satiety ratings before the ad libitum meal were lower on MG2 than in ZH and increased back to baseline on MG4, the ratings given after the meal did not change significantly between ZH and MG2, but were higher on MG4 compared with MG2 ($p < 0.05$). Total energy intake was negatively correlated with AMS scores on MG2 ($p = 0.043$, $r = -0.468$), but not on MG4, and it was not correlated with sO_2 on any of the study days. Similarly, in a stepwise multiple regression, the only significant predictor for energy intake on MG2 was AMS (LLS $p = 0.042$, $\beta = -0.471$). BMI, age, gender and sO_2 were not significant.

Effect of dexamethasone on energy intake

In total, 11 subjects were treated with dexamethasone on the evening of MG2 (nine with AMS and two HAPEs without AMS). Energy intake was lower at baseline in ZH in those subjects who later received dexamethasone treatment for AMS and/or HAPE susceptibility after study procedures on MG2 (treated 712 ± 382 kcal vs. untreated:

Table 3 Hunger/satiety scores on a 100-mm visual analog scale directly before (pre-meal) and after (post-meal) the ad libitum meal ($n = 22$)

	ZH		MG2		MG4	
	Pre-meal	Post-meal	Pre-meal	Post-meal	Pre-meal	Post-meal
Hunger (mm)	59 ± 8	34 ± 7	43 ± 8	31 ± 7	64 ± 6^b	41 ± 7^b
Desire to eat (mm)	58 ± 8	37 ± 7	40 ± 7^a	30 ± 7	65 ± 6^b	40 ± 7^b
Amount of food (mm)	59 ± 7	42 ± 6	42 ± 6^a	33 ± 6	61 ± 5^b	42 ± 6^b

ZH Zurich, low altitude, 446 m; *MG2* Capanna Margherita day 2, first examination day at high altitude, 4,559 m; *MG4* Capanna Margherita day 4, second examination at high altitude

[a] Significantly different compared to ZH ($p < 0.05$)

[b] Significantly different compared to MG2 ($p < 0.05$)

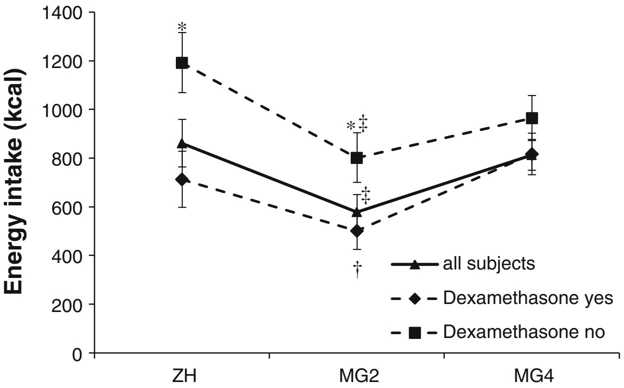

Fig. 2 Difference in energy intake at the ad libitum dinner between subjects treated with dexamethasone on the evening of MG2 ($n = 11$) and untreated subjects ($n = 11$). *Indicates significant differences compared with the 'dexamethasone yes' group ($p < 0.05$); †indicates significant difference compared to MG4; ‡indicates significant differences compared with ZH and MG4; the *error bars* are standard error of the mean

1,192 ± 410 kcal; $p = 0.010$), but the pattern of change over the days was similar in both groups (Fig. 2). Energy intake was also lower on MG2 in the subjects that had to be treated with dexamethasone (treated 501 ± 243 kcal vs. untreated 802 ± 306 kcal; $p = 0.029$; note: treatment started only after the ad libitum dinner on that day), but it did not differ between groups on MG4 (treated 817 ± 283 kcal vs. untreated 964 ± 307 kcal; $p = 0.255$). Acclimatization and dexamethasone treatment significantly contributed to increase energy intake from MG2 to MG4 ($p = 0.006$ in the non-treated, $p = 0.015$ in the treated subjects).

Food preferences

Liking

Liking scores of the different food categories (high fat, low fat, sweet and savory) are presented in Table 4. Liking for high-fat, low-fat and savory foods was significantly increased on MG4 compared with MG2 ($p < 0.05$); the difference between MG4 and ZH was only significant for savory foods ($p < 0.05$). For sweet foods, no significant differences were detected between days. A negative correlation of liking scores for low-fat and savory foods on MG2 (pre-meal) with AMS was present ($p = 0.009$, $r = -0.569$ and $p = 0.013$, $r = -0.546$, respectively), while none of the scores were related to AMS on MG4.

A stepwise multiple regression model was used to investigate the effect of liking of the different food categories, and it revealed that for all days, liking for high-fat foods was a predictor of total energy intake (ZH: $p < 0.001$, $b = 0.763$, $R^2 = 0.582$; MG2: $p = 0.008$, $b = 0.588$, $R^2 = 0.346$ and MG4: $p = 0.012$, $b = 0.527$, $R^2 = 0.277$), while all other food categories and dexamethasone were not significant predictors.

Relative preference

The mean frequencies of food choices for the four categories are shown in Table 4. For all categories, frequencies did not differ between the days, but they differed between pre- and post-meal ($p < 0.01$). For high-fat and sweet foods, the frequency increased after food intake while it decreased for low-fat and savory food on all days. Further, a significant positive association between sweet frequency (pre-meal) and AMS was seen on MG2 ($p = 0.044$, $r = 0.466$).

To assess the relationship between measures of food choice and energy intake, two independent composite scores were created: relative taste preference: sweet frequency—savory frequency; relative macronutrient preference: high-fat frequency—low-fat frequency. Stepwise multiple regression models revealed that relative preference measures and dexamethasone treatment were not predictors of energy intake on any of the days.

Gastrointestinal and pancreatic hormones

Blood samples were not available on all days from four of the 25 subjects. The plasma concentrations of glucagon, amylin, peptide tyrosine–tyrosine (PYY) and cholecystokinin

Table 4 Mean liking ratings on a 100-mm visual analog scale and mean frequency of food choice for different food categories in a fasted state (before the preload) and after the ad libitum meal on all three examination days ($n = 22$)

	ZH		MG2		MG4	
	Pre-meal	Post-meal	Pre-meal	Post-meal	Pre-meal	Post-meal
Liking score						
High fat	42.0 ± 22.1	21.7 ± 14.8[c]	34.5 ± 17.0	21.6 ± 15.4[c]	46.1 ± 19.6[b]	27.6 ± 15.2[c]
Low fat	44.0 ± 15.5	22.8 ± 14.4[c]	42.6 ± 18.5	22.7 ± 15.1[c]	48.4 ± 12.3[b]	29.1 ± 15.3[a,c]
Sweet	32.7 ± 19.8	26.7 ± 16.2	25.8 ± 15.8	26.1 ± 21.8	29.4 ± 16.1	30.8 ± 19.4
Savory	53.3 ± 22.2	17.8 ± 17.1[c]	51.4 ± 24.1	18.3 ± 16.5[c]	63.1 ± 18.9[a,b]	25.9 ± 17.1[a,c]
Frequency of choice						
High fat	28.4 ± 5.1	32.1 ± 4.1[c]	28.4 ± 5.8	30.1 ± 4.2[a,c]	28.4 ± 5.8[b]	30.3 ± 4.5[a]
Low fat	31.6 ± 5.1	27.9 ± 4.2[c]	32.9 ± 6.9	30.0 ± 4.1[a,c]	21.5 ± 5.7	29.7 ± 4.5[a]
Sweet	20.4 ± 6.2	36.9 ± 10.0[c]	19.3 ± 6.6	36.9 ± 11.1[c]	18.5 ± 6.8	34.1 ± 12.6[c]
Savory	39.5 ± 6.2	23.1 ± 10.0[c]	39.6 ± 8.3	23.1 ± 10.9[c]	41.3 ± 6.7	25.8 ± 12.5[c]

ZH Zurich, low altitude, 446 m; *MG2* Capanna Margherita day 2, first examination day at high altitude, 4,559 m; *MG4* Capanna Margherita day 4, second examination at high altitude

[a] Significantly different compared to ZH ($p < 0.05$), paired samples *t* test

[b] Significantly different compared to MG2 ($p < 0.05$), paired samples *t* test

[c] Significantly different compared to pre-meal on the same day ($p < 0.05$), paired samples *t* test

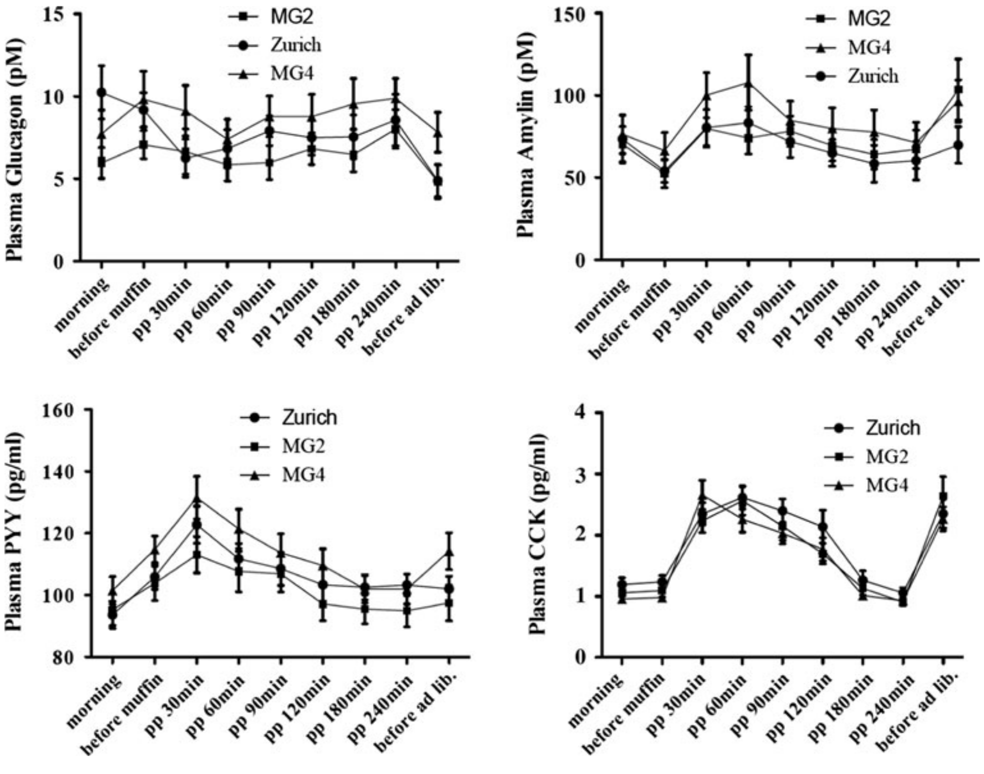

Fig. 3 Plasma concentrations of glucagon, amylin, peptide tyrosine–tyrosine (PYY) and cholecystokinin (CCK) over the entire study day at the different examination days in healthy subjects ($n = 19$–21). *Zurich* low altitude, 446 m; *MG2* Capanna Margherita day 2, first examination day at high altitude, 4,559 m; *MG4* Capanna Margherita day 4, second examination at high altitude; $n = 21$

(CCK) on the different study days and time points are presented in Fig. 3. No significant changes in plasma glucagon or gastrin concentrations were observed in response to food intake or on the different days. Plasma amylin, PYY and CCK increased postprandially but did not differ between days.

Overall altitude increased amylin and PYY ($p < 0.05$), but there were no significant effects for individual differences between days at any time point. Except for glucagon and CCK, the area under the curve (AUC) throughout the postprandial period did not significantly differ between days for any of the hormones.

Glucagon output was decreased postprandially (negative AUCs) and the AUC for 240 min was significantly smaller on MG4 compared with ZH ($p = 0.023$). Furthermore, in the immediate (60 min) postprandial period, the AUC for glucagon was smaller on MG2 compared with ZH ($p = 0.043$), whereas the difference between MG4 and ZH was not significant. The short-term response (30 and 60 min) of CCK was greater on MG4 compared with ZH ($p < 0.05$), but there was no difference between ZH and MG2.

A non-significant trend was observed for amylin to be increased on MG2 throughout the postprandial phase and for PYY to be reduced on MG2 in the early postprandial phase.

Discussion

This study presents a detailed assessment of dietary intake and dietary preferences with measurements of gastrointestinal and pancreatic hormones in 22 healthy human subjects on exposure to acute hypoxia following rapid ascent from 446 m to 4,559 m. As expected, a marked decrease in oxygen saturation indicative of severe hypoxia was present after rapid ascent to high altitude with a fall in sO_2 from 97 % at low altitude to 76 % on the first day at high altitude. At the same time, 39 % of the participants experienced AMS symptoms that required treatment with dexamethasone. The findings demonstrate that rapid ascent to high altitude influences eating behavior in several different ways. Compared with the baseline examination in Zurich (ZH), results for the first-day examination at high altitude (MG2) showed (1) a significant reduction in energy intake by 33 % in the ad libitum meal, (2) reduced hunger and desire to eat scores and increased satiety ratings, which correlated with the reduced energy intake, and (3) altered food preferences where liking for all except sweet foods was reduced.

Energy intake

The reduced energy intake at 4,559 m confirms the previous findings at similar altitudes where both men and women were shown to reduce their energy intake by more than 30 % after ascent to 4,300–5,100 m [15, 21, 33, 40]. The present study extends these findings by providing a systematic analysis of certain factors that may contribute to the energy intake reducing the effect of hypoxia following rapid ascent to high altitude. These include the presence of AMS symptoms and changes in baseline or postprandial release of neuroendocrine gastrointestinal hormones that influence energy intake and gastrointestinal function.

We demonstrated that energy intake on MG2 was reduced and negatively correlated with AMS scores. Interestingly, not only scores above the threshold for diagnosis of AMS but even subclinical scores of AMS were associated with energy intake; this can also be seen by the fact that energy intake was reduced to a similar extent in both the treated and the non-treated groups. Energy intake returned to near normal levels on MG4, when also the association with AMS scores was no longer present. Differences between MG2 and MG4 cannot be attributed only to acclimatization as 48 % of subjects were treated with dexamethasone after study procedures ended on the evening of MG2. Nevertheless, acclimatization or adaptation appears to play an important role as the day-by-day increase in energy intake was also observed in the non-treated group. This is in agreement with the previous studies which have shown that subjects can learn to eat adequate amounts and that this can, during a longer exposure, prevent or at least attenuate excessive weight loss [4]. In contrast to AMS scores, there was no direct association between hypoxemia and energy intake on any study day. Thus, reduced energy intake after rapid ascent to high altitude may not be determined by hypoxia *per se*, but rather by the individual's susceptibility to AMS. Only one previous study reported on the association between AMS and energy intake and found no significant correlation [25]. In this study, however, the sample size was very small (7 subjects), and they trekked to 4,700 m within 10 days as compared to the 2 days in our study. The slower ascent may have allowed for gradual acclimatization and thus a different response to hypoxia.

Food preferences

We also studied changes in food preferences that may be associated with reduced eating in hypoxic conditions at high altitude, an assessment that, to our best knowledge, was never done in this form before. Liking ratings for high-fat foods assessed before the meal were good predictors for energy intake, independent of day and altitude; however, neither changes in liking nor changes in relative food preference ratings were predictors for changes in total energy intake from baseline to high altitude. Thus, overall, food preference is not the major cause of reduced energy intake at high altitude although it may have some impact. There were however significant effects on specific food items. Palatability (liking) of all food items except for sweet food was reduced after a meal at baseline and at high altitude. This confirms that the strong hedonic response induced by sweet foods may override homeostatic signals of satiety [9]. More interestingly, and in contrast to the previous studies [27, 31], we also noted a significant increase in the palatability of savory foods at high altitude and an interaction between food preferences and susceptibility to AMS. This increase may be related to sodium depletion after 3 days exertion at high altitude. Sodium depletion in humans and rats leads to an increased palatability of salt [2, 34], and it is known that ascent to high altitudes leads to sodium diuresis linked to a suppression of the renin-angiotensin-aldosterone system [42]. This effect was weaker in patients with AMS. Indeed, there was a positive correlation between the frequency for sweet foods and a negative correlation for savory foods with AMS scores on MG2. Thus, in contrast to subjects that remain well at altitude, subjects that develop AMS seem to prefer sweet foods over savory foods. These effects may be mediated through homeostatic mechanisms involving renin-angiotensin-aldosterone system that control sodium balance. Such mechanisms also have been linked to performance at altitude and survival on intensive care [26]. In consequence, during expeditions to high altitude, individual food choices may reflect underlying physiologic adaptation to hypoxia and may, potentially, influence the likelihood of developing AMS.

Gastrointestinal neuroendocrine hormones

The release of anorexigenic neuroendocrine hormones such as glucagon, amylin CCK and PYY from the gastrointestinal tract after a meal is considered to play a key role in meal-ending satiation [10], but their role in reduced eating at high altitude is less clear. Results for glucagon are contradictory; whereas an animal study in rats demonstrated increased glucagon secretion under hypoxic conditions (simulated altitude of 5,000 m) [6], a human study found decreased concentrations at high altitudes (7,134 m) [5]. In our study, there was no change in glucagon plasma levels between baseline and high altitude on MG2 or on MG4. We also observed no significant increase in the postprandial glucagon concentration and no differences between test days. These negative results may be due to the relatively low protein content of the muffin lunch (400 kcal, 9.9 g protein), which may be below the level required to stimulate a substantial glucagon release [17]. Indeed, against our expectations, postprandial AUC for glucagon were even negative, indicating a decrease in glucagon secretion after food intake on all examination days. This argues against a major role of glucagon in reduced eating during the ad libitum dinner on MG2, although the limitations noted above apply.

The anorexigenic hormone CCK has been shown to be increased in human subjects on the second day after ascent to 5,100 m [1]; this increase has been linked to the hypoxia-inducible factor (HIF) [1, 13]. In contrast to these findings, we did not see significant differences in plasma CCK concentrations between samples taken at baseline in Zurich and on any of the 2 days at high altitude. Of note, even though the altitude was similar in both studies, the duration of ascent varied considerably. While our subjects ascended to 4,559 m in only 2 days, the subjects in the other study climbed to 5,100 m in 20 days, providing much more time for acclimatization not only to hypoxia but also to exertion. Interestingly, the AUCs for CCK, indicative of total CCK output, were significantly higher on MG4 in the early postprandial phase (0–30 or 0–60 min), whereas there was no change on MG2. Because eating was significantly reduced on MG2, where no change in CCK was observed, but not on MG4, it seems unlikely that altered CCK secretion contributed to the changes in food intake in this setting.

The contribution of PYY, amylin or gastrin to reduced eating in hypoxic conditions has not been studied previously. Similar to glucagon and CCK, all three hormones are implicated in the control of energy intake; however, no significant differences in any of these hormones were observed between the three examination days. Further, there were no significant differences in the AUCs between test days for amylin and PYY, neither over the entire postprandial period nor for shorter time intervals.

Overall, it therefore appears unlikely that changes in the secretion of the neuroendocrine hormones studied here are involved in the reduced dietary intake documented after rapid ascent to 4,559 m.

Limitations of this study include difficulty differentiating the effect of hypoxia on eating behavior from the effect of exertion. Subject activity on ZH, MG2 and MG4 test days was tightly controlled, but there was no equivalent prior to the ZH test day to the rapid ascent to high altitude on MG1. Nevertheless, even though a short-term reduction in hunger and energy intake has been observed directly following intense exercise [39], the normal longer-term response to physical activity is to increase energy intake [36], and the opposite was observed on MG2. Thus, if anything, the results may underestimate the effects of hypoxia on appetite and energy intake. Similar to most nutritional studies, forced eating patterns were applied, and the size of muffin test meals was not adapted to the energy requirements of the subjects. Furthermore, the muffin meal may not have been adequate to provoke normal postprandial changes in gastrointestinal hormones, and the sample size may have been too small, as certain non-significant trends were observed. Finally, the use of dexamethasone in some study participants certainly affected the results on MG4. Due to ethical concerns, it was not possible to randomize the subjects into treated and non-treated groups during a 5-day stay at 4,559 m; all subjects showing severe AMS symptoms on the evening of MG2 were treated. It is important to mention, however, that only one participant required steroid treatment prior to the measurements on MG2 and that the analysis found similar trends in each subgroup.

In conclusion, our data suggest that reduced food intake after rapid ascent to high altitudes was mediated by a variety of factors, which are still not completely understood. Reduced energy intake under hypoxic conditions at altitude was independently related to both reduced appetite before the meal and the presence of AMS symptoms. Altered food preferences were also present, although they were probably not the main drive. Changes in energy intake and food preferences were not related to altered secretion of gastrointestinal hormones under the current experimental conditions and, thus, the underlying mechanism by which hypoxia exerts its effects on appetite, and eating behavior remains uncertain. One possible mechanism that was not explored here would be a reduction in appetite mediated by elevated serum leptin concentrations that have been found previously at high altitudes [35]. Furthermore, plasma sodium was found to be reduced in subjects suffering from AMS at high altitude as a result of reduced urine flow and thus a dilution through total body water [18]. However, whether this would directly affect food intake or appetite or whether changes in sodium intake might affect severity of AMS was not studied.

Treatment with dexamethasone was an effective approach for reversing AMS symptoms and improving energy intake. Whether the prophylactic administration of steroids prior to ascent might help to prevent the early decrease in food intake, remains to be determined.

These findings may also be relevant to understand the effects of hypoxia in other conditions. Using the model of high-altitude studies for achieving a better understanding of the effect of hedonic and homeostatic systems in the control of appetite and energy intake in a hypoxic state might also help in the nutritional management of patients suffering from respiratory diseases, although it remains to be determined whether the mechanisms are truly comparable.

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Conflict of interest The authors declare that they have no conflict of interest.

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