

RESEARCH ARTICLE

# Endocrine responses and food intake in fasted individuals under the influence of glucose ingestion

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## Abstract

### Introduction

Different metabolic conditions can affect what and how much we eat. Hormones of glucose metabolism and adipokines such as adiponectin take part in the control of these decisions and energy balance of the body. However, a comprehensive understanding of how these endocrine and metabolic factors influence food intake has not been reached. We hypothesised that the amount of food a person consumes differs substantially after a fasting period even after the energy deficit was partially removed by glucose ingestion and endocrine signals like insulin and C-peptide indicated a high glucose metabolic status. Furthermore, the macronutrient composition of the consumed food and a possible association with adiponectin under the influence of glucose ingestion was assessed.

### Methods

In a within-subject design, 24 healthy males participated in both a fasting (42 h) and control (non-fasting) condition. A total of 20 blood samples from each subject were collected during each condition to assess serum levels of adiponectin, insulin, C-peptide, cortisol and ACTH. At the end of each condition food intake was measured with an ad libitum buffet after the acute energy deficit was compensated using a carbohydrate-rich drink.

### Results

The total amount of caloric intake and single macronutrients was higher after the fasting intervention after replenishment with glucose. All recorded hormone levels, except for adiponectin, were significantly different for at least one of the study intervals. The relative proportions of the macronutrient composition of the consumed food were stable in both conditions under the influence of glucose ingestion. In the non-fasting condition, the relative amount of protein intake correlated with adiponectin levels during the experiment.

## OPEN ACCESS

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## Discussion and conclusion

An anabolic glucose metabolism after glucose ingestion following a fasting intervention did not even out energy ingestion compared to a control group with regular food intake and glucose ingestion. Anorexigenic hormones like insulin in this context were not able despite higher levels than in the control condition to ameliorate the drive for food intake to normal or near normal levels. Relative macronutrient intake remains stable under these varying metabolic conditions and glucose influence. Serum adiponectin levels showed a positive association with the relative protein intake in the non-fasting condition under the influence of glucose although adiponectin levels overall did not differ in between the conditions.

## Introduction

Both obesity and its associated metabolic disorders have become a global health burden in recent years [1]. Excessive calorie intake and macronutrient composition of consumed food are major factors in the development of this obesity pandemic [2–5]. Therefore, investigation into the quantity and food composition an individual consumes and why may assist in developing a more comprehensive understanding of how metabolic disorders develop.

The amount of food we consume is regulated by a balance of orexigenic and anorexigenic influences on areas of the central nervous system [6]. This balance is determined by a large number of interneuronal and endocrine signalling substances [7–9]. How these factors are computed in the resulting hunger, satiety and overall energy intake and which factors are the most dominant in this equation is not well understood. Hormones involved in the control of glucose metabolism are likely to be part of these crosslinks, and insulin is understood to be one of the factors that act as an anorexigenic signal [10]. How big the influence of single aspects of these regulatory processes like hormones of glucose metabolism is remains uncertain.

Previous studies in rodents found differences in food selection after short fasting periods [11], however it has not yet been investigated whether the same would occur in humans after the acute energy shortage has been partly compensated. Short-term energy status of the body is reflected by hormones like insulin and C-peptide while corticosteroids play a fundamental role in control of glucose metabolism. To which degree the physiological release of insulin as a response to raising glucose levels in the blood after ingestion of carbohydrates can ameliorate feelings of hunger is unknown.

While the quantity of food consumed appears to be the central factor in development of obesity [5], the quality of its components seems to wield some influence as well. Studies suggest that the composition of macronutrients an individual chooses before initiating a therapeutic diet has implications for the diet's success [12] and similarly that the composition of the therapeutic diet influences diet outcomes and physiological parameters [13,14]. Furthermore, it has been shown that the variation in macronutrient composition of consumed food results in different hormonal responses [15] which might regulate satiety and hunger signals, as well as the choice of macronutrients one prefers. One of these hormones is adiponectin whose serum levels vary after diets as a function of fat and carbohydrate content of the diet [16,17]. Other hormones associated with glucose metabolism, such as insulin [18] and cortisol [19,20], have also been found to be influenced by different macronutrient compositions.

Nevertheless, the interplay between metabolic conditions, hormonal responses and food intake is not well understood and especially little is known about the interplay of

macronutrient intake, endocrine factors and absolute energy intake. Most studies examine the effect of diets and food composition on endocrine parameters, food consumption and weight loss. Essential parts of the puzzle, such as hormones regulating the size of the meal and the specific composition of macronutrients, might therefore be missing [21]. Also, the regulation of macronutrient intake in different metabolic situations and long-term deficits or excesses is largely unknown. It has been shown that there are efficient compensatory mechanisms that are unlikely to be explained by fluctuation of hormones with fast kinetics [22]. Adipokines with slower kinetic characteristics may play a major role in this context [23].

To address the questions of how energy deficits control our eating behaviour even if energy deficits have been partially removed by glucose ingestion was the aim of this study. Additionally, it was attempted to find out if adiponectin, one of the emerging major players in the understanding of the metabolic syndrome, plays a role in the regulation of non-acute food intake and its composition under the metabolic conditions that apply in our experiment.

To fill in some of the research gaps, we measured the amount and composition of food consumed after a period of fasting or non-fasting (control); and after acute metabolic energy deficits were at least partly compensated for by oral ingestion of a large load of carbohydrates. It was hypothesised that fasting might still have implications on total food intake after the partial compensation of energy shortage by ingestion of glucose and the resulting alterations of hormones concerned with glucose metabolism towards an anabolic status. To induce insulin and C-peptide levels as high as possible after the glucose administration in the fasting condition to evaluate their role on appetite control as clearly as possible, studies that showed fasting induced glucose intolerance were used to determine the length of the fasting period [24,25]. These studies usually used fasting periods around 70 hours. After consultation with the ethics committee of the University of Luebeck we decided that a fasting period of 42 hours would be ideal in terms of combining the aims of likelihood of producing high insulin and C-peptide levels, safety and practicability. Furthermore, it was hypothesised that an association of the proportions of consumed food with adiponectin levels might exist in this context. This study focussed on a limited array of hormones because they were predominantly important to assess the impact of the oral glucose administration, due to reasons of practicability and the available means.

## Materials and methods

### Participants

24 healthy male participants of normal weight and without metabolic disease were enrolled for the study [age (mean  $\pm$  SEM): 24.5  $\pm$  0.6 years; body mass index (mean  $\pm$  SEM): 23.4  $\pm$  0.3 kg/m<sup>2</sup>]. Participants were not on any medication and had a regular self-reported sleep-wake cycle for 6 weeks before participating in the experiment. Individuals with acute or chronic diseases, drug abuse including alcohol (> 5 drinks per week) and smoking or exceptional physical activity were excluded. We also excluded individuals with special eating behaviours, e.g. vegetarians and vegans. The night before the experiment, the participants were asked to go to bed at approximately 11 p.m. and to avoid any exhausting physical activity. The study abided by the Declaration of Helsinki and was approved by the Ethics Committee of the University of Lübeck. All subjects gave written informed consent.

### Experimental setting

A within subject design with two conditions was used. Half of the participants started with the condition of total caloric deprivation (fasting condition = FAST) and the other half with the control condition (non-fasting = EAT). Conditions were spaced exactly 7 days apart.

Experiments started on the first day at 8 a.m. with participants arriving at the sleep laboratory of the Department of Psychiatry which is equipped to host long-term studies. For the fasting condition, participants were instructed to refrain from eating from 11 p.m. the evening before. In the control condition participants were provided with a standardised meal by the study team. Subsequently, an antecubital venous catheter was inserted for blood samples and half an hour later the first blood samples were obtained.

Afterwards, participants in the non-fasting condition had a standardized breakfast (2240 kcal, 14% proteins, 46% fat, 40% carbohydrates) followed by regular standardized meals (on average: 1320 kcal, 17% proteins, 31% fat, 51% carbohydrates); and during these meals, further blood samples were obtained. Overall 20 blood samples were obtained per condition over the two days of the experiment (blood samples were taken at 08:45 a.m., 10:00 a.m., 12:45 p.m., 02:00 p.m., 04:00 p.m., 06:00 p.m., 06:45 p.m., 08:00 p.m. and 10:00 p.m. on the first day and 08:45 a.m., 10:00 a.m., 11:45 a.m., 01:00 p.m., 01:35 p.m., 02:15 p.m., 02:45 p.m., 03:15 p.m., 03:45 p.m., 04:15 p.m. and 04:45 p.m. on the second day in both conditions). Participants were provided with oral glucose (polysaccharides dissolved in 300 mg of water that are broken down to 75g of glucose in the intestines; Accu-Chek Dextrose O.G.-T. 300 ml, Roche Diagnostics, ELISA, Indianapolis, IN, USA) at 1:30 p.m..

A standardized buffet was provided at 05:00 p.m. with a wide variety of offered foods and drinks. The participants were allowed to choose freely for one hour [26]. Food intake was measured and macronutrient composition as well as overall energy intake could be calculated for each individual. A list with detailed information about the food offered in the buffet can be found in the supplementary material [S5 Dataset](#).

The experiment ended at 6 p.m. with the end of the buffet. The subjects in the fasting condition spent 42 hours in total without any caloric intake. No blood samples were obtained during the night-time to keep disturbance of physiological rhythms as minimal as possible. The subjects stayed at the study venue over the whole time of the experiment in single rooms and spend the night there as well with members of the study team being present over the whole time.

## Assays

Blood samples were centrifuged immediately after they were obtained, and the supernatant was stored at  $-80^{\circ}\text{C}$ . The measurement of all hormones took place at the same point of time to avoid inter-assay variabilities. Blood serum and EDTA (Ethylenediaminetetraacetic acid) plasma were used to measure the hormone levels through an immunoassay. The ACTH-assay (Roche Diagnostics, ELCIA, Indianapolis, IN, USA) had a measuring range of 0.220–440 pmol/L, an intra-assay coefficient of variation (CV) of  $< 2.4\%$  and an inter-assay CV of  $< 4.2\%$ . The C-peptide-assay had a measuring range of 0.003–13.3 nmol/L, an intra-assay CV of  $< 4.6\%$  and an inter-assay CV of  $< 5.0$ . The Insulin-assay had a measuring range of 1.39–6945 pmol/L, an intra-assay CV of  $< 2.8\%$  and an inter-assay CV of  $< 4.9\%$ . Cortisol had a measuring range of 0.5–1750 nmol/L, an intra-assay CV of  $< 2.9\%$  and an inter-assay CV of  $< 4.7\%$ . Adiponectin levels were measured with an Adiponectin ELISA (Immundiagnostik AG, Adiponectin total ELISA Kit, Bensheim, Germany) with an intra-assay CV of  $< 3.4\%$  and inter-assay CV of  $< 6.3\%$ .

## Statistical analysis

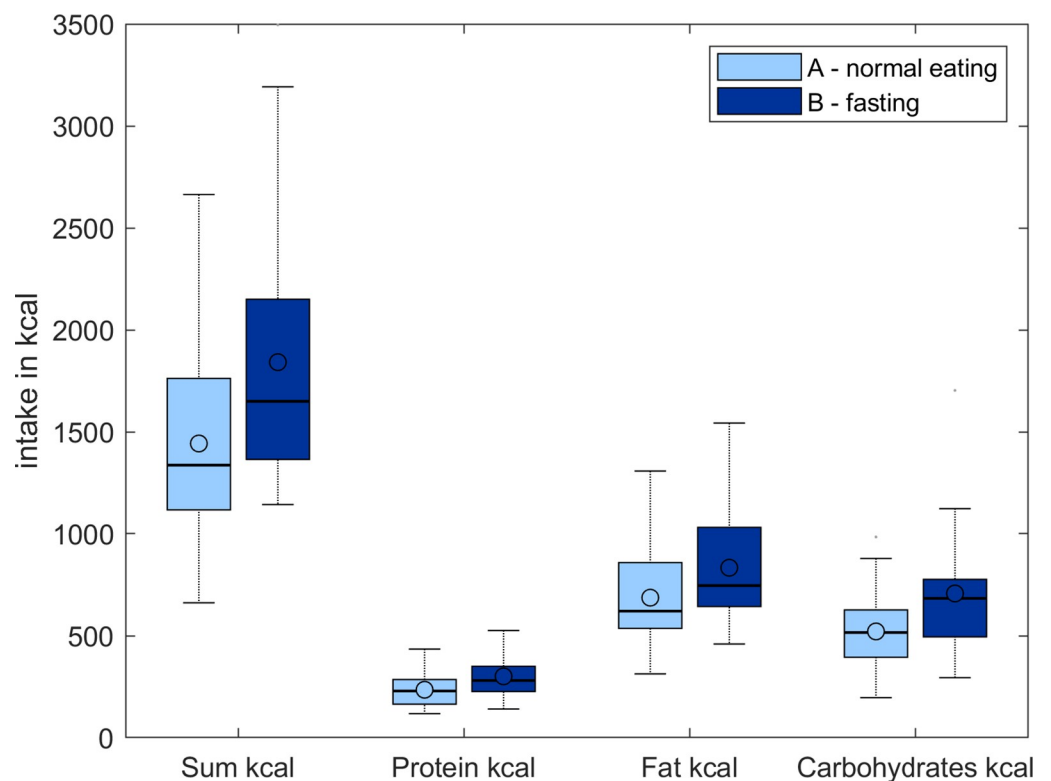
MATLAB 2015a and SPSS version 23 were used for data preparation and statistical analysis. All data is presented as mean values  $\pm$  SEM. Comparison of consumed food composition was carried out with paired student t-tests. The area under the curve (AUC) of the time course of

the blood concentration of adiponectin was calculated with trapezoidal assumptions for the whole time of the experiment. A multiple stepwise linear regression with the individual AUC-values of adiponectin as a dependent variable and the relative quantities of the consumed macronutrient fat, carbohydrates and protein in the buffet test as independent variables was performed for each condition. For the comparison of the hormonal levels and plasma glucose levels within the different conditions, factorial ANOVAs were performed for all timepoints (timepoint, tp 1–20) and split into two parts—before the administration of oral glucose (tp 1–13) and afterwards (tp 14–20) to control for differences in the phases of the experiment. Significance was assumed for p-values <0.05.

## Results

### Buffet

The total number of kilocalories and the overall amount of each macronutrient consumed differed significantly between the conditions (Fig 1). Absolute food consumption was higher in the fasting group for all measured variables including the total amount of food (EAT: 1442.7 ±496.7 kcal; FAST: 1841.5±618.7 kcal; t(23) = 5.2, p<0.001), protein (EAT: 235.1±85.2 kcal; FAST: 300.9±103.6 kcal; t(23) = 5.4, p<0.001), fat (EAT: 686.7±262.5 kcal; FAST: 833.5±270.6 kcal; t(23) = 3.8, p = 0.001) and carbohydrates(EAT: 521±191.5 kcal; FAST: 707.2±302.5 kcal; t(23) = 3.7, p<0.001). However, the proportion of macronutrients in kilocalories showed no significant statistical difference between both conditions. Both conditions consumed the same percentage of proteins (16%, t(23) = 0.06, n.s.) and relatively similar percentages of fat (48% in



**Fig 1. Food consumption during the buffet after 42 hours of fasting and the control condition.** Box Plots of the total food consumption in the buffet scenario for both fasting and normal eating condition. The total amount of kilocalories and the overall amount of each macronutrient consumed differed significantly between the conditions.

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the non-fasting condition and 45% in the fasting condition,  $t(23) = 1.3$ , n.s.) and carbohydrates (36% in the non-fasting condition and 38% in the fasting condition,  $t(23) = 1.2$ , n.s.).

### Hormones and blood glucose

Repeated measures ANOVAs including all 20 measurement timepoints revealed a main effect of conditions for insulin ( $F(1,23) = 27.7$ ,  $p < 0.001$ ), C-peptide ( $F(1,23) = 62.2$ ,  $p < 0.001$ ) and ACTH ( $F(1,23) = 4.7$ ,  $p = 0.042$ ) but not for cortisol ( $F(1,23) = 2.8$ , n.s.), glucose ( $F(1,23) = 1.2$ , n.s.) and adiponectin ( $F(1,23) = 3.3$ , n.s.). When the timepoints were separated into pre-oral glucose (tp 1–13) and post-oral glucose (tp 14–20), a significant difference was found for insulin (pre:  $F(1,23) = 371.9$ ,  $p < 0.001$ ; post:  $F(1,23) = 12.6$ ,  $p = 0.002$ ), C-peptide (pre:  $F(1,23) = 331.8$ ,  $p < 0.001$ ; post:  $F(1,23) = 19.2$ ,  $p < 0.001$ ) and glucose (pre:  $F(1,23) = 30.5$ ,  $p < 0.001$ ; post:  $F(1,23) = 42.8$ ,  $p < 0.001$ ) in both sectors. Cortisol only showed significant differences in the post-oral glucose sector (pre:  $F(1,23) = 0.024$ , n.s.; post:  $F(1,23) = 7.6$ ,  $p = 0.01$ ). Both adiponectin (pre:  $F(1,23) = 2.8$ ,  $p = 0.11$ ; post:  $F(1,23) = 2.9$ ,  $p = 0.1$ ) and ACTH (pre:  $F(1,23) = 2.4$ ,  $p = 0.14$ ; post:  $F(1,23) = 2.9$ ,  $p = 0.1$ ) did not show any significant differences in either sector. Figs 2 and 3 show the time courses of all measured serum parameters.

### Correlations of adiponectin and food intake

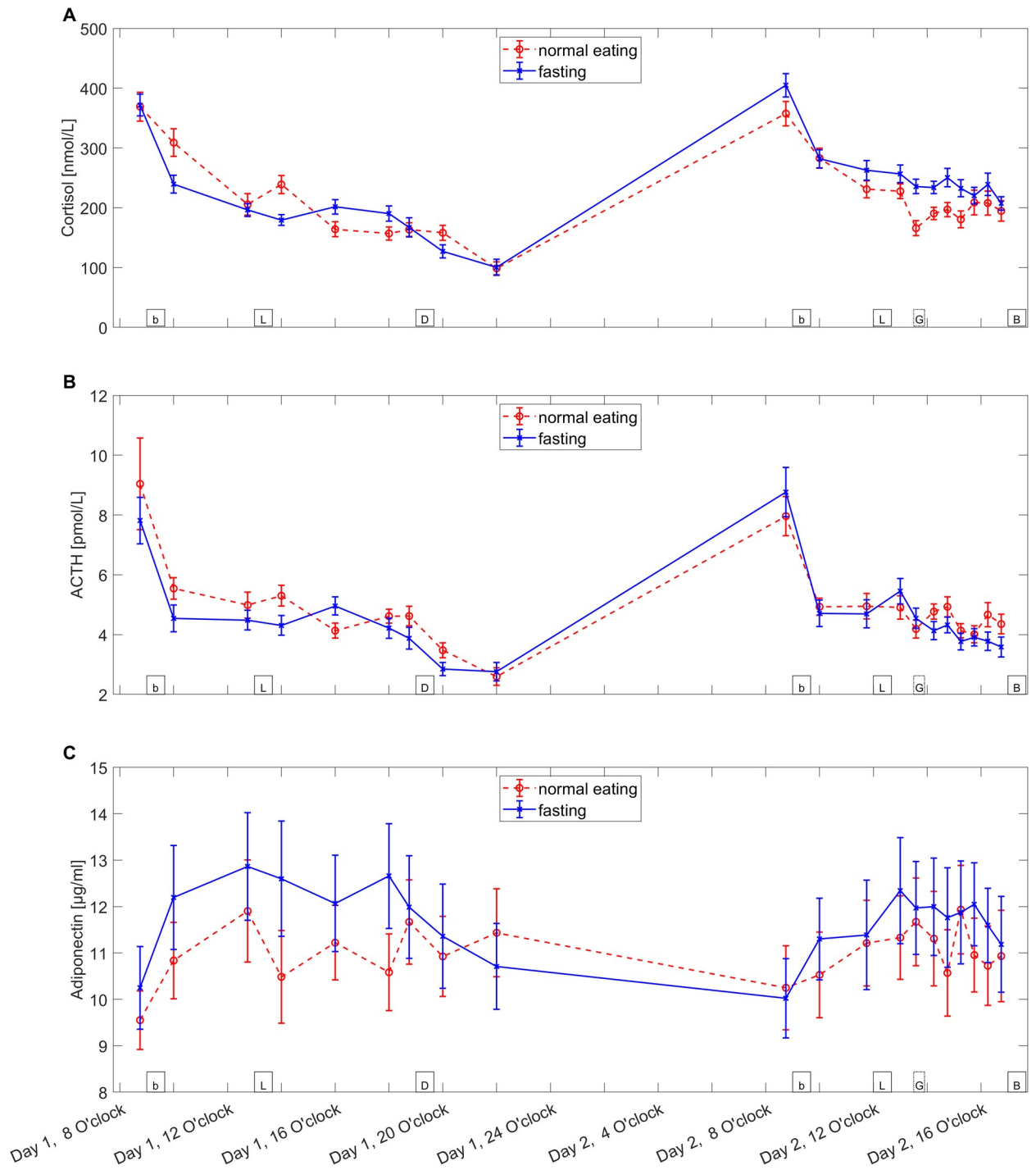
A significant regression equation was found for the predictor relative protein content in the control condition ( $F(1,22) = 6.4$ ,  $p = 0.19$ ) with an  $R^2$  of 0.22 when the AUC-values of adiponectin were used as a dependent variable. No significant regression equation was found for the fasting condition.

### Discussion

This study compared food intake after either fasting or non-fasting periods when an acute caloric deficit was partially removed by oral glucose towards the end of the experiment. Whereas the total quantity of food ingested differed between conditions, the relative proportion of each macronutrient consumed did not. The relative amount of protein intake in the non-fasting condition correlated positively with the AUC-value of adiponectin throughout the experiment.

The observed increase in energy intake following a period of energy restriction has been described before [22,27,28] and appears to be intuitively the expected result. These studies suggest that there is a compensatory increase in overall energy intake after a period of caloric restriction as opposed to when individuals are not fasted. No previous study determined whether similar results would be obtained if the acute caloric deficit was compensated by the means of administering a large quantity of carbohydrates. Also the question whether the relative proportion of macronutrients consumed changes between fasting and non-fasting conditions has not been tackled previously.

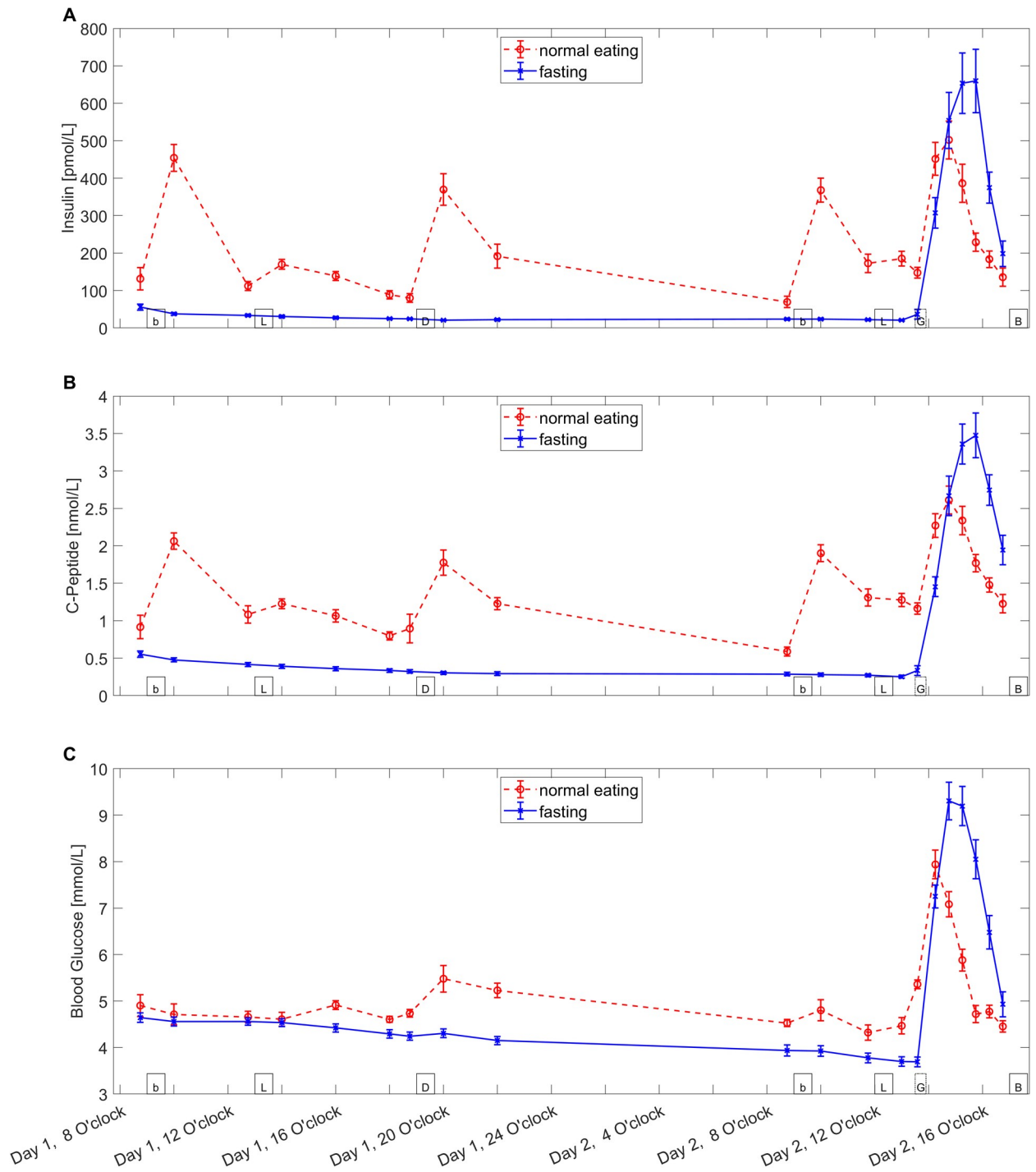
Studies in obese subjects suggested that a compensatory increase in energy intake after a short energy restricted period does not occur [27,29], whereas data obtained in normal weight individuals tend to find an overall compensatory increase in energy intake after energy restriction thus corroborating the current results. This current experiment extended previous results by showing that food ingestion was increased after fasting in spite of application of oral glucose. The overall energy deficit of the body appeared to be driving overall energy consumption, even though insulin, C-peptide and serum glucose had higher levels in the fasting conditions at this time than in the control-condition. These higher levels reflect the well described phenomenon of “post-fasting glucose intolerance” [25,24]. In our case, this phenomenon shows



**Fig 2. Levels of cortisol (A), ACTH (B) and adiponectin (C).** The Figure shows the mean  $\pm$  standard error of the mean for both fasting (blue line, crosses) and normal eating (red spotted line, circles) condition of the serum parameters during the experiment. Boxes on the bottom of the graph indicate the timepoints of meals (b = breakfast, L = lunch, D = Dinner, G = oral glucose administration, B = Buffet).

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that these parameters are unlikely to be the only factors providing the brain with feedback about the energy status of the body.



**Fig 3. Levels of insulin (A), C-peptide (B), blood glucose (C).** The Figure shows the mean  $\pm$  standard error of the mean for both fasting (blue line, crosses) and normal eating (red spotted line, circles) condition of the serum parameters during the experiment. Boxes on the bottom of the graph indicate the timepoints of meals (b = breakfast, L = lunch, D = Dinner, G = oral glucose administration, B = Buffet).

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The relative macronutrient proportions of the ad libitum consumed food were not significantly different in between the conditions. We stress the fact that the results of the assessment of the macronutrient composition were only assessed in the context of the pre-meal glucose



drink. The administration of the glucose was necessary to test for the main outcome of overall energy intake after a 42 caloric restriction after partial compensation with carbohydrates. Since there was no additional non-replenishment control group the influence of the glucose on the composition of food can't be determined by this experiment. Further research is needed to confirm this finding and to determine whether the administered glucose might have affected this measurement as it has been shown that administering carbohydrates before a meal can have an influence on food choice. It has been shown before that carbohydrates can increase subsequent food consumption [30]. Thus, further evaluation of the influence a carbohydrate enriched diet has on food choice is needed. Furthermore, there are other possibilities why the food choice was driven into a certain direction. Some of the food items might have been more appetible than others due to their size or looks. Also, parts of the food were offered in a heated state, which might have directed attention towards these food items. Nevertheless, the stability of the proportions of food consumed under the different metabolic conditions remains noteworthy.

Adiponectin concentration did not differ between the conditions in this study. Due to the short but total caloric restriction, this result is in line with previous work showing that short total caloric restriction for 72 hours does not alter adiponectin levels over time [31]. It has also been shown that low caloric diets do not interfere with adiponectin levels for short [32] and intermediate [33] time periods providing that weight loss is minimal. Usually only long term fasting that results in meaningful weight loss results in rising adiponectin levels [34,35]; and recent work in rodents shows that caloric restriction for four weeks increases adiponectin expression on a cellular level [36]. Of note, declining adiponectin levels during fasting interventions have also been reported [37]. The duration of our study was too short to show alterations in levels of a hormone with slow kinetics such as adiponectin. It therefore supports current literature suggesting a very low diurnal and post-prandial biovariability of adiponectin [38], even when sweetened beverages were offered with normal meals [39].

The proportion of consumed proteins correlated with adiponectin levels only in the non-fasting condition. While existing evidence usually deals with the influence of dietary interventions on adiponectin levels [17,40,41], our finding may hint at a role of adiponectin level in food choice, i.e. macronutrient composition. Indeed, there is evidence adiponectin may take part in appetite regulation in the central nervous system [42,43]. However, whether adiponectin has an appetite stimulating [40] or attenuating role [41] remains controversial. The fact that our experiment did not show a difference in adiponectin levels during the experiment makes it less likely that the detected statistical association is derived from a physiological causal mechanism and overall harder to interpret the finding. No change in both adiponectin levels and macronutrient intake in between conditions while the associations only exists in one of the conditions does not leave any room for causal conclusions. However, different metabolic conditions might also alter the influence of endocrine signals on ingestive behaviour and adiponectin might exercise control differently over central nervous function in a fasting metabolic state than in a normally nourished one. Further research will be needed to evaluate the role of adiponectin in this context. Additionally, with regard to the relationship between adiponectin and protein intake, it has to be stressed that the direction of causality cannot fully determined by the current experiment. Although the adiponectin concentrations were measured before the buffet which might indicate that adiponectin was the cause and the protein intake the effect, as pointed out before, adiponectin has rather slow kinetic characteristics making reverse causality a possible option for the interpretation of the data.

Further limitations of this study include that neither women nor people outside an average weight range were included. Thus, these results might not extend to groups other than young, healthy normal weight men. Moreover, the oral glucose administration prior to the

administration of the buffet test might have masked effects of fasting on food choice. Future studies might also explore to administer a more tailored quantity of glucose to compensate the energy deficit more precisely, which was not attempted in our study. This study measured only a limited number of hormones directly involved in glucose metabolism and one adipokine that has been shown before to be influenced by the composition of food. Further research into other endocrine signal parameters such as CCK, glucagon, GLP-1, ghrelin and leptin in this context will be needed to gain a more comprehensive understanding of quantity and quality of food intake.

## Supporting information

**S1 Dataset. Buffet fasting condition.** Macronutrients consumed during the buffet after the fasting condition in kilocalories.  
(TXT)

**S2 Dataset. Buffet control condition.** Macronutrients consumed during the buffet after the control condition in kilocalories.  
(TXT)

**S3 Dataset. Hormones fasting condition.** Hormones and blood glucose measured at 20 time-points each in the fasting condition.  
(TXT)

**S4 Dataset. Hormones control condition.** Hormones and blood glucose measured at 20 time-points each in the control condition.  
(TXT)

**S5 Dataset. Contents of buffet.** Detailed list of contents of the standardised buffet the subjects could choose from at the end of the experiment.  
(XLSX)

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**Conceptualization:** Janis Marc Nolde, Arkan Al-Zubaidi, Marcus Heldmann, Thomas F. Münte, Kamila Jauch-Chara.

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**Writing – original draft:** Janis Marc Nolde.

**Writing – review & editing:** Janis Marc Nolde, Arkan Al-Zubaidi, Marcus Heldmann, Thomas F. Münte, Kamila Jauch-Chara.

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