



## Effects of blood glucose on delay discounting, food intake and counterregulation in lean and obese men



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### ARTICLE INFO

#### Keywords:

Delay discounting  
Impulsivity  
Glucose metabolism  
Hypoglycemia counterregulation  
Food intake  
Obesity

### ABSTRACT

**Background:** Delay discounting as a measure of impulsivity has been shown to be higher in obesity with an association of increased food intake. Moreover, obese humans showed a higher wanting for high-calorie food than lean men when blood glucose concentrations were low. First studies linking blood glucose levels to delay discounting yielded mixed results. We hypothesized that obese people – in comparison to lean men – have a relative lack of energy, especially when blood glucose levels are low, that results in higher levels of delay discounting, food intake and hormonal counterregulation.

**Methods:** We investigated 20 lean and 20 obese healthy young men in a single-blind balanced cross-over design. With a standardized glucose clamp technique, subjects underwent a hypoglycemic state in one condition and a euglycemic state in the control condition. Regularly, blood was sampled for assessment of hormonal status, and questionnaires were filled out to assess delay discounting and symptom awareness. After normalizing blood glucose concentrations, subjects were free to eat from a standardized test buffet, followed by a snack test.

**Results:** Delay discounting was higher in obese than in lean men throughout experiments ( $p < 0.03$ ). However, we did not observe significant discounting differences between glucose conditions ( $p > 0.1$ ). Furthermore, the discounting performance did not correlate with food intake from the test buffet or snack test ( $p > 0.3$ ). As a response to hypoglycemia, hormonal counterregulation was pronounced in both weight groups ( $p < 0.03$ ), but responses of ACTH, norepinephrine and glucagon were stronger in obese compared to lean men ( $p < 0.03$ ). Also, intake from the high-calorie buffet after hypoglycemia compared to euglycemia was higher in obese subjects ( $p < 0.02$ ) but comparable in lean men ( $p > 0.5$ ).

**Conclusions:** Our data suggest that augmented delay discounting is a robust feature in obesity that is not linked to glucose levels or actual food intake. With our systematically controlled approach, combining performance in delay discounting with regard to distinct blood glucose levels, different weight groups, counterregulatory behavior and food intake, our results imply that delay discounting is not susceptible to fluctuations of blood glucose and do not support the assumption that a low body's energy content leads to increased impulsivity. Further replications including women and larger sample sizes are needed to corroborate our data.

### 1. Introduction

Given the increasing number of overweight and obesity, the understanding of the reasons for unhealthy diets is important (Collaborators et al., 2017). 'Delay discounting' is discussed as a marker of self-control and impulsivity that receives growing attention as a possible factor for unhealthy choices (Barlow et al., 2016; Story et al., 2014). People who 'discount' the value of the reward in the future,

prefer smaller immediate rewards over larger rewards available after a delay. Relating to food intake, some unhealthy foods rich in sugar and fat offer immediate reward, whereas healthy diets may offer delaying benefits like maintaining weight, which let researchers hypothesize a link between individual delay discounting rates and food intake (Barlow et al., 2016). Several studies revealed a positive association of delay discounting rates with total energy intake (Appelhans et al., 2012; Rollins et al., 2010), frequency of fast food consumption (Garza et al.,

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2016) and body mass index (Ikeda et al., 2010; Jarmolowicz et al., 2014; Weller et al., 2008).

At present, there is a lively debate about the link between impulsivity or self-control and the body's glucose content. Wang and Dvorak could demonstrate lower discount rates in participants with elevated blood glucose levels, leading to speculations that a higher body-energy budget may result in more future orientated decisions (Wang and Dvorak, 2010; Wang and Huangfu, 2017). This is in line with the assumption that self-control failures are more likely when glucose is low or cannot be mobilized effectively to the brain (Gailliot and Baumeister, 2007; Gailliot et al., 2007). Interestingly, Page et al. have demonstrated that blood glucose modulates neural control over food motivation and suggested that this restraining influence of glucose is lost in obesity (Page et al., 2011). Despite these first results, recent studies questioned the influence of blood glucose levels on delay discounting and self-control. Ingestion or oral sensing of glucose did not affect self-control performance in men and women (Boyle et al., 2016; Lange and Eggert, 2014). These results let researchers doubt if human brain functioning can really be impaired by the negligible amount of glucose consumed during self-control tasks and they appealed for independent replications investigating the role of glucose for self-control (Dang, 2016; Lange and Eggert, 2014; Orquin and Kurzban, 2016; Vadillo et al., 2016). Further studies are also challenged to explore the influence of glucose per se by directly manipulating glucose levels compared to the oral ingestion of glucose that bares the risk of influence by factors like taste, expectations or gastrointestinal side effects. To take these aspects into account, we directly influenced glucose levels with the glucose clamp procedure as the gold standard to obtain two distinct states of blood glucose (hypoglycemia vs. euglycemia) by infusing glucose and insulin without any cognitive bias provoked by ingestion.

In our study, we aimed at shedding light on this discussion, investigating with a systematic approach the link between (a) delay discounting performance, (b) highly distinguished blood glucose levels, (c) hormonal and symptomatic counterregulation as a measure of neuglycopenia, i.e., the mobilization of glucose to the brain, (d) subsequent food intake, and (e) different weight groups. Therefore, we used the glucose clamp procedure in lean and obese men and assessed parameters of counterregulation, food intake and delay discounting performance. Based on the studies mentioned above, we hypothesized that low blood glucose levels would enhance impulsivity as indicated by increased delay discounting rates and thereby increase food intake. Based on the positive association of delay discounting and BMI and on the assumption that obese people are more prone to a lack of glucose, we further hypothesized that obese people – in comparison to lean men – show an even enhanced response towards low blood glucose levels with higher levels of delay discounting and increased hormonal counterregulation.

## 2. Materials and methods

### 2.1. Participants

Twenty lean men (mean  $\pm$  SEM age:  $24.9 \pm 0.6$  years; BMI:  $22.2 \pm 0.4$  kg/m<sup>2</sup>) and twenty obese men (mean age:  $25.4 \pm 0.8$  years; BMI:  $36.8 \pm 1.4$  kg/m<sup>2</sup>) of Caucasian descent participated in the experiments ( $p > 0.5$  for age,  $p < 0.002$  for BMI for group comparisons). Physical or mental disease, and abuse of alcohol, nicotine or drugs were excluded by medical history, physical examination, and laboratory tests. Other exclusion criteria were nightshifts, exceptional stress during the past two weeks, and fasting blood glucose levels  $> 6.1$  mmol/l to exclude prediabetes. The study was approved by the ethics committee of the University of Lübeck (reference number 12-171) and all subjects provided their written informed consent before participation.

### 2.2. Experimental design and clamp procedure

Each subject participated in two sessions (euglycemic and hypoglycemic clamp), separated by an interval of at least two weeks. The study was performed in a single-blind design and the order of the sessions was balanced across subjects.

After an overnight fast, participants arrived at the medical research unit at 7:45 a.m. Experiments took place in a sound attenuated room with the subjects resting on a bed. One venous catheter was placed in each arm. Both cannulas were connected to long thin tubes that enabled blood sampling and the infusion of glucose and insulin from an adjacent room without the awareness of the subject. A microphone and video camera were installed for communication and observation purposes.

After a 90 min baseline period, at 09:15 a.m., an insulin bolus of 10 mU/kg body weight of human insulin (Insuman<sup>®</sup> Rapid, Sanofi-Aventis, Frankfurt, Germany) was administered for two minutes followed by a constant rate infusion of 1.5 mU/kg/min. Glucose concentrations were measured every five minutes in whole blood (HemoCue, Ängelholm, Sweden) and a solution of 20% glucose was infused at variable rates. Blood pressure, heart rate and physical well-being were continuously monitored. After 45 min, at 10:00 a.m., glucose target concentrations were achieved (target concentrations of  $\sim 100$  mg/dl for the euglycemic session and  $\sim 50$  mg/dl for the hypoglycemic session). These concentrations were maintained for 45 min. During this time, the study participant filled out the questionnaires for delay discounting and symptom awareness. At 10:40 a.m., insulin infusion was stopped, and euglycemia was re-established by infusion of glucose within the next 30 min. Thereafter, subjects were offered a rich test buffet for the next 30 min, followed by a snack test lasting 10 min.

Blood samples were drawn every 10 min during the plateau and every 30 min before and after the plateau to determine concentrations of plasma glucose, insulin, c-peptide, ACTH, cortisol, growth hormone, glucagon, and catecholamines. Blood samples were centrifuged and plasma as well as serum were stored at  $-80$  °C until assay.

### 2.3. Delay discounting task and symptom scores

For assessing delay discounting, participants performed a 27-item Monetary Choice Questionnaire (MCQ) once during baseline (09:00 a.m.) and once during the euglycemic or hypoglycemic plateau (10:30 a.m.). This established questionnaire measures delay discounting by asking individuals to choose between smaller rewards available immediately and larger rewards available after a delay (Kirby et al., 1999). Individual indifference points were determined and discounting rates (overall k-values) calculated using an excel-based spreadsheet tool provided by Kaplan et al. (2016). Logarithmic transformations of k-values were performed to approximate a normal distribution for use with parametric statistical analyses.

Subjective symptom awareness was rated on a 10-point scale twice during baseline, twice during the plateau, and once after finishing the test buffet. The questionnaire assesses symptoms that have previously shown to be sensitive to hypoglycemia and can be grouped into neuroglycopenic symptoms (dizziness, tingling, blurred vision, difficulty in thinking, faintness) and autonomic symptoms (anxiety, palpitation, hunger, sweating, irritability, tremor (Mitrakou et al., 1991)).

### 2.4. Analyses of blood parameters

Plasma glucose was measured in fluoride plasma (Roche-Diagnostic, Grenzach, Germany). Routine assays were used for the measurements of insulin, C-peptide, cortisol, adrenocorticotropic hormone (ACTH), human growth hormone (hGH) (all Immulite, Siemens, Erlangen, Germany) and glucagon (RIA, IBL International, Hamburg, Germany). Plasma epinephrine and norepinephrine concentrations were measured by standard high-performance liquid chromatography (Chromsystems, Munich, Germany).

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