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Glycemic increase induced by intravenous glucose infusion fails to affect hunger, appetite, or satiety following breakfast in healthy men

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ABSTRACT

Meal-dependent fluctuations of blood glucose and corresponding endocrine signals such as insulin are thought to provide important regulatory input for central nervous processing of hunger and satiety. Since food intake also triggers the release of numerous gastrointestinal signals, the specific contribution of changes in blood glucose to appetite regulation in humans has remained unclear. Here we tested the hypothesis that inducing glycemic fluctuations by intravenous glucose infusion is associated with concurrent changes in hunger, appetite, and satiety. In a single blind, counter-balanced crossover study 15 healthy young men participated in two experimental conditions on two separate days. 500 ml of a solution containing 50 g glucose or 0.9% saline, respectively, was intravenously infused over a 1-h period followed by a 1-h observation period. One hour before start of the respective infusion subjects had a light breakfast (284 kcal). Blood glucose and serum insulin concentrations as well as self-rated feelings of hunger, appetite, satiety, and fullness were assessed during the entire experiment. Glucose as compared to saline infusion markedly increased glucose and insulin concentrations (peak glucose level: 9.7 ± 0.8 vs. 5.3 ± 0.3 mmol/l; $t(14) = -5.159$, $p < 0.001$; peak insulin level: 370.4 ± 66.5 vs. 109.6 ± 21.5 pmol/l; $t(14) = 4.563$, $p < 0.001$) followed by a sharp decline in glycaemia to a nadir of 3.0 ± 0.2 mmol/l (vs. 3.9 ± 0.1 mmol/l at the corresponding time in the control condition; $t(14) = -3.972$, $p = 0.001$) after stopping the infusion. Despite this wide glycemic fluctuation in the glucose infusion condition subjective feelings of hunger, appetite satiety, and fullness did not differ from the control condition throughout the experiment. These findings clearly speak against the notion that fluctuations in glycemia and also insulinemia represent major signals in the short-term regulation of hunger and satiety.

1. Introduction

Glucose is the brain's most important fuel and is traditionally been thought to represent a key metabolic signal in the regulation of eating behavior (Mayer, 1952). In the brain, glucose availability is continuously sensed by glucose-sensitive and glucose-responsive neurons that are mainly located in hypothalamus (Burdakov, Luckman, & Verkhratsky, 2005; Karnani & Burdakov, 2011) and brain stem (Ritter, Dinh, & Zhang, 2000). Depending on glucose availability, respective neurons modulate the release of anorexigenic and orexigenic neuropeptides such as NPY (Morton, Meek, & Schwartz, 2014). In the body periphery, circulating glucose concentrations are continuously sensed by specific cells located in the portal vein, gut veins, and the bulbus caroticus which report respective information to the brain via neuronal afferences (Adachi, Shimizu, Oomura, & Kobáshi, 1984; Hevener, Bergman, & Donovan, 2001; Liu, Seino, & Kirchgessner, 1999; Pardal & López-Barneo, 2002). However, experiments in animals do not support a role of

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neuronal glucose sensing in the regulation of feeding behavior under normal physiological, non-glucopenic conditions (Dunn-Meynell et al., 2009; Levin, 2007; Levin, Routh, Kang, Sanders, & Dunn-Meynell, 2004). Although acute fluctuations in blood glucose have been discussed to be involved in meal initiation and postprandial satiety, scientific evidence for a general role of circulating glucose levels in the regulation of hunger, satiety and appetite in humans, although often implied, is not unequivocal (Flint et al., 2006; Melanson, Westerterp-Plantenga, Saris, Smith, & Campfield, 1999).

Acute hypoglycemia as a state of central nervous energy deprivation has been repeatedly shown to provoke feelings of hunger (Schultes et al., 2003) and to selectively enhance the processing of food stimuli (Brody, Keller, Degen, Cox, & Schächinger, 2004; Schultes et al., 2005a, 2005b). Even short-term hypoglycemia during nocturnal sleep increases caloric intake at a breakfast buffet served to healthy men on the next morning (Schmid et al., 2008). In patients with type 2 diabetes, which is characterized by chronic hyperglycemia, the acute normalization of circulating glucose levels by insulin infusion has been shown to provoke an increase in food intake in an experimental setting (Schultes et al., 2005c). Furthermore, increasing circulating glucose levels to about 15 mmol/l, i.e. hyperglycemic level that is usually only seen in subjects with diabetes, enhances satiety in healthy volunteers. Interestingly this effect appears to be predominantly mediated by glucose and not insulin concentrations since hyperinsulinemic euglycaemia in this study did not affect satiety (Gielkens, Verkijk, Lam, Lamers, & Masclee, 1998). However, conflicting data exist on the effects of less pronounced hyperglycemia, i.e. glucose levels of 8–10 mmol/l, induced by continuous intravenous glucose infusion on appetite regulation. While in one study no effect on hunger and satiety ratings was observed (Lavin et al., 1996), another study found an increase in feelings of fullness under the condition of mild hyperglycemia (Andrews, Rayner, Doran, Hebbard, & Horowitz, 1998). Furthermore, another study failed to detect any effect of mild hyperglycemia of hunger and fullness ratings, but found a 15% reduction in subsequent food intake as compared to a euglycemic control condition (Chapman, Goble, Wittert, Morley, & Horowitz, 1998).

In addition to direct effects on glucose sensors, fluctuations in circulating glucose concentration might contribute to appetite regulation by triggering concomitant changes in secretion patterns of the glucoregulatory hormone insulin, which itself exerts effects on appetite regulation (Woods, Lutz, Geary, & Langhans, 2006). Applying the approach of intranasal insulin administration to specifically determine central nervous effects of the hormone without eliciting strong peripheral metabolic effects (Born et al., 2002), we have previously shown that insulin delivered to the human brain acutely decreases food intake in the fasted state (Benedict, Kern, Schultes, Born, & Hallschmid, 2008), increases satiety while reducing snack intake in the postprandial period (Hallschmid, Higgs, Thienel, Ott, & Lehnert, 2012), and in men decreases body fat content during long-term administration. Furthermore, a meta-analyses of a serious of meal test studies has indicated that the incremental postprandial increase in circulating insulin rather than glucose levels is associated with feelings of hunger and satiety as well as with prospective food intake (Flint et al., 2007).

In the present study we intended to further elucidate the role of circulating glucose dynamics in short-term appetite regulation. In order to avoid, as much as possible, a biasing influence of glucose-associated gastrointestinal hormone modulation, we systematically manipulated glycaemia by intravenous glucose infusion rather than by an oral glucose load. We hypothesized that exogenously induced glycemic fluctuations that are in their extent similar to postprandial glucose excursions are associated with concurrent changes in hunger, appetite, and satiety.

2. Methods

2.1. Subjects

We studied 15 healthy men aged 20–40 years (mean ± SEM: 25.1 ± 0.6 years) with a body mass index between 20.2 and 25.1 kg/m^2 (22.8 ± 0.4 kg/m^2). Exclusion criteria were chronic or acute illness, current medication of any kind, smoking, alcohol or drug abuse, obesity and diabetes in first degree relatives. All subjects reported regular eating habits including regular intake of a breakfast meal and did not follow a specific diet (e.g. vegetarian diet). Also, subjects were screened for restraint eating behavior by the three-factor eating questionnaire (Stunkard & Messick, 1985) and subjects showing a score above 10 (of 21) on the cognitive restraint scale were excluded from the study. Importantly, the subjects were not informed about the primary purpose of the study, i.e. the assessment of feelings of satiety/hunger and appetite, but were told that the study would focus on metabolic variables as blood glucose and insulin concentrations. The ethics committee of the University of Lübeck approved the study protocol and all participants gave written informed consent.

2.2. Study design and procedure

Participants were tested in a single blind, counter-balanced crossover design on two conditions spaced at least two weeks apart. In one condition the subjects received a 10% glucose infusion and a 0.9% saline infusion in the other condition (control condition) according to the protocol outlined below.

On each experimental day subjects arrived at the research unit at 07:00 h. They were instructed to eat a light dinner on the preceding evening and then to stay fastened overnight. During the 3-h assessment period (08:00 h - 11:00 h) the subjects were allowed to read non-arousing books or play video games that did not contain any food cues. At 07:20 h two intravenous catheters were inserted in two veins of the subject's distal forearms to allow infusions and the drawing of blood samples. At 08:00 h subjects ate a light breakfast, i.e. two cereal bars (Corny Cereal Bar, Schwartauer Werke GmbH, Bad Schwartau, Germany; in total 218 kcal; 3.4 g protein, 31.6 g carbohydrate, 8.6 g fat). The rather low caloric content of the light breakfast was chosen to avoid a ceiling effect on hunger as well as on satiety (both directions) that would have precluded the detection of glucose infusion effects.

In the glucose infusion condition, a total of 500 ml 10% glucose solution (50 g glucose, i.e. 200 kcal) was infused between 09:00 h–10:00 h, whereas a total of 500 ml NaCl 0.9% was infused continuously during the experimental session in the control condition. Blood glucose was measured online (HemoCue B-Glucose-Analyzer, Ángelholm, Sweden) in 30-min intervals before the start of the glucose infusion and in 15-min intervals thereafter. The subjects were kept unaware of their current blood glucose concentration. Blood samples were drawn at 07:30 h (baseline), 08:00 h, 09:00 h, 10:00 h, and 11:00 h, centrifuged and the serum supernatant was stored at −80 °C until assay. Serum insulin concentrations were determined by enzyme-linked immunoassays as described previously (Schmid et al., 2007).

Immediately before each blood drawing, subjects rated autonomic and neuroglycopenic symptoms from 0 (none) to 9 (severe) on a standardized semi-quantitative symptom questionnaire (Fruehwald-Schultes et al., 2001) that included the target symptoms hunger, appetite (as a further and idiomatic term for "hunger" in German), satiety, and fullness the remaining 23 symptoms of the