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

Bernd Schultes[1], Ann-Kristin Panknin[2], Manfred Hallschmid[3,4,5], Kamila Jauch-Chara[6], Britta Wilms[2], Felix de Courbière[2], Hendrik Lehnert[2,7], and Sebastian M. Schmid*[2,7]

[1]*eSwiss Medical & Surgical Center, Brauerstrasse 97, CH-9016 St. Gallen, Switzerland*

[2]*Department of Internal Medicine I, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany*

[3]*Department of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Otfried-Müller-Str. 25, 72076 Tübingen, Germany*

[4]*German Center for Diabetes Research (DZD), Tübingen, Germany*

[5]*Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tübingen (IDM), Tübingen, Germany*

[6]*Department of Psychiatry and Psychotherapy, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany*

[7]*German Center for Diabetes Research (DZD), Lübeck, Germany*

* Address correspondence to:

Sebastian M. Schmid, M.D.

Email: Sebastian.Schmid@uksh.de

not for publication:
Fon: 0049-(0) 451-500 5096
Fax: 0049-(0) 451-500 3818
Running title: Glycemic fluctuation and appetite regulation

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-hour period followed by a 1-hour observation period. One hour before start of the respective infusion subject 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 conditions 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.

Keywords: Blood glucose, insulin, nutritional sensing, satiety, hunger, appetite

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 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, Oltmanns, Kern, Fehm, Born, & Peters, 2003) and to selectively enhance the processing of food stimuli (Brody, Keller, Degen, Cox, & Schächinger, 2004; Schultes, Kern, Oltmanns, Peters, Gais, Fehm, & Born, 2005a; Schultes, Peters, Kern, Gais, Oltmanns, Fehm, & Born, 2005b). Even short-term hypoglycemia during nocturnal sleep increases caloric intake at a breakfast buffet served to healthy men on the next morning (Schmid, Jauch-Chara, Hallschmid, Oltmanns, Born, & Schultes, 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, Wittert, Sun, Horowitz, Morley, & Read, 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, Lange, Kern, McGregor, Bickel, & Fehm, 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.

Methods

Subjects

We studied 15 healthy men aged 20 to 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.

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-hour 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, Hallschmid, Jauch-Chara, Bandorf, Born, & Schultes, 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 questionnaire served to distract the subjects' attention from hunger-related symptoms (data not shown).

Statistical analyses

All values are expressed as means±SEM. Analyses of blood parameters as well as symptom ratings were based on ANOVA for repeated measures, including the factor 'condition' (for the comparison of glucose infusion vs. control condition) and 'time' (for the repeated measurements during the experiment). For pair-wise comparisons Student's t-test was used. A p-value <0.05 was considered significant.

Results

Circulating glucose and insulin concentrations

Before the intake of the snack meal, there were no differences between the glucose infusion and the saline infusion condition with regard to blood glucose (4.3±0.1 mmol/l vs. 4.3±0.2 mmol/l, $t(14) = -0.022$, $p=0.98$) and serum insulin (28.5±5.8 pmol/l vs. 22.7±2.6 pmol/l, $t(14) = 0.931$, $p=0.37$) concentrations. As expected, during the experiment marked differences in circulating glucose and insulin levels between conditions were observed ($F(3, 14) = 32.14$ and $F(1, 14) = 18.51$, respectively, both $p<0.001$ for ANOVA 'condition' x 'time' interaction term, Figure 1). In the saline infusion condition, subjects showed an increase in glucose and insulin levels in response to the light breakfast that peaked at 09:00 h (glucose: 5.3±0.3 mmol/l; insulin: 109.6±21.5 pmol/l). In contrast, during glucose infusion circulating concentrations of glucose and insulin steeply rose and remained significantly higher than in the control condition until 10:00 h ($t(14) < 6.900$, $p<0.001$ for all glucose comparisons; $t(14) < 4.900$, $p<0.004$ for all insulin comparisons). Peak levels in the glucose infusion condition were 9.7±0.8 mmol/l for glucose (at 09:30 h) and 370.4±66.5 pmol/l for insulin (at 10:00 h). After the end of the glucose infusion at 09:55 h circulating glucose concentrations sharply decreased and at 10:45 h and 11:00 h reached levels that were even lower than in the control condition ($t(14) < -3.374$, $p<0.005$ for both comparisons). Nadir glucose levels were 3.0±0.2 mmol/l in the glucose infusion condition and 3.9±0.1 mmol/l in the control condition ($t(14) = -3.972$, $p=0.001$). Insulin concentrations at 11:00 h had returned to a level that was not significantly different from the saline infusion condition anymore.

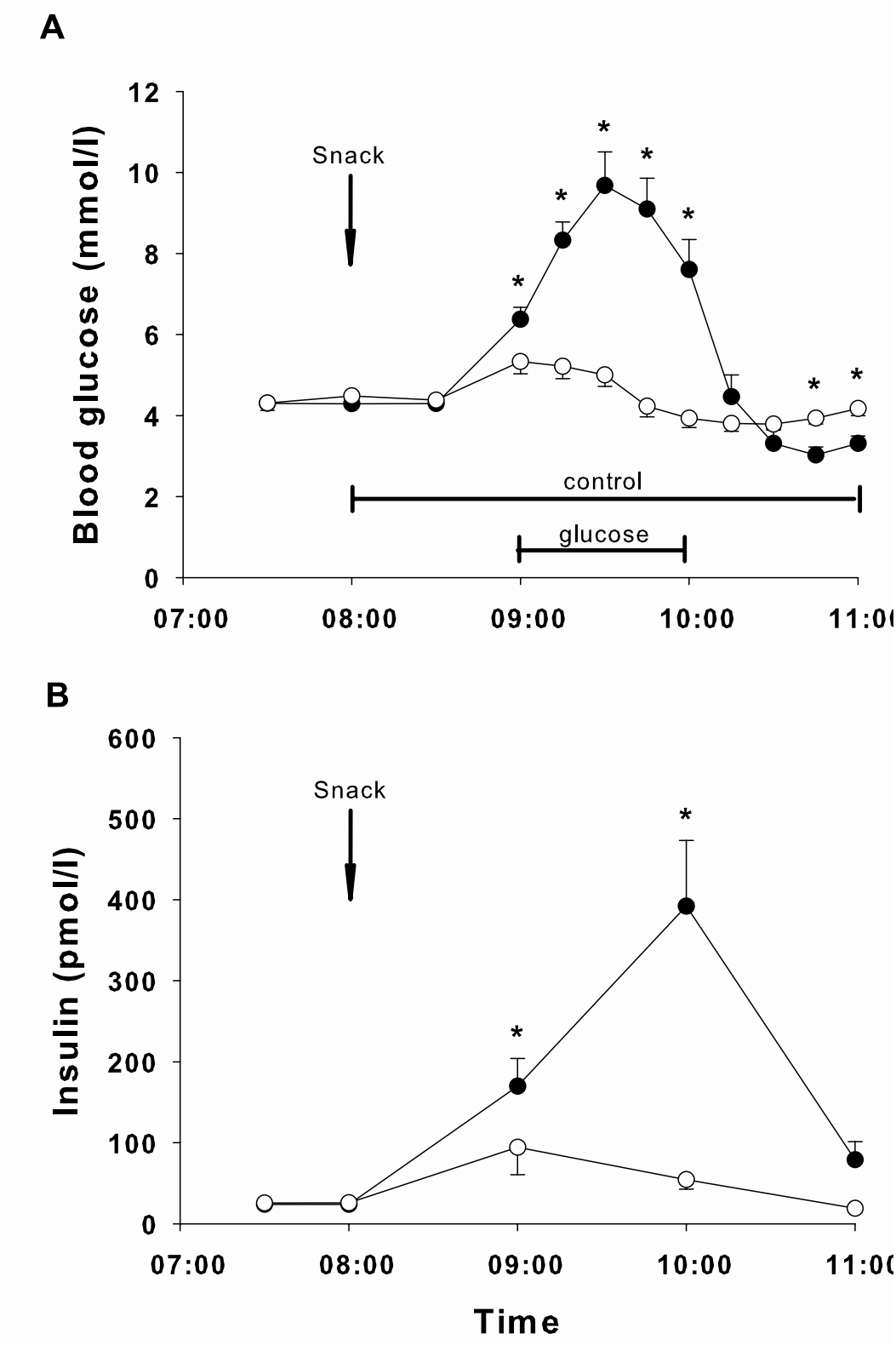

Figure 1: Mean (± SEM) concentrations of (A) blood glucose and (B) serum insulin in 15 healthy men during a total period of 270 minutes with either a 60 min infusion of 500 ml 10% glucose solution (black circles) or a continuous infusion of 500 ml 0.9% NaCl (open circles). The arrow indicates ingestion of the breakfast snack of 218 kcal at 08:00 h while horizontal lines indicate the periods of respective infusions. *$p<0.05$.

Hunger, appetite, satiety, and fullness ratings

Self-rated hunger, appetite, satiety, and fullness did not differ in the morning of both experimental conditions ($t(14) > -0.725$, $p > 0.67$ for all comparisons; Figure 2). After the intake of the light breakfast, ratings on hunger and appetite in both conditions showed a slight (non-significant) temporal decrease with a nadir at 09:00 h followed by a progressive increase until the end of the experiment ($F(2, 14) = 9.929$ and $F(3, 14) = 8.849$, respectively, both $p < 0.001$ for ANOVA main effect 'time'). Satiety ratings in both conditions showed a temporal increase peaking at 09:00 h followed by a gradual decrease ($F(2, 14) = 4.626$, $p = 0.020$ ANOVA main effect 'time'). Fullness ratings remained unchanged during the entire experiment in both conditions ($F(2, 14) = 2.409$, $p = 0.12$ ANOVA main effect 'time'). None of the self-rated symptoms differed between conditions (fullness $F(1, 14) = 0.299$, satiety $F(3, 14) = 0.787$, hunger $F(3, 14) = 0.020$, appetite $F(3, 14) = 0.242$, all $p > 0.47$ for ANOVA 'condition' x 'time' interaction).

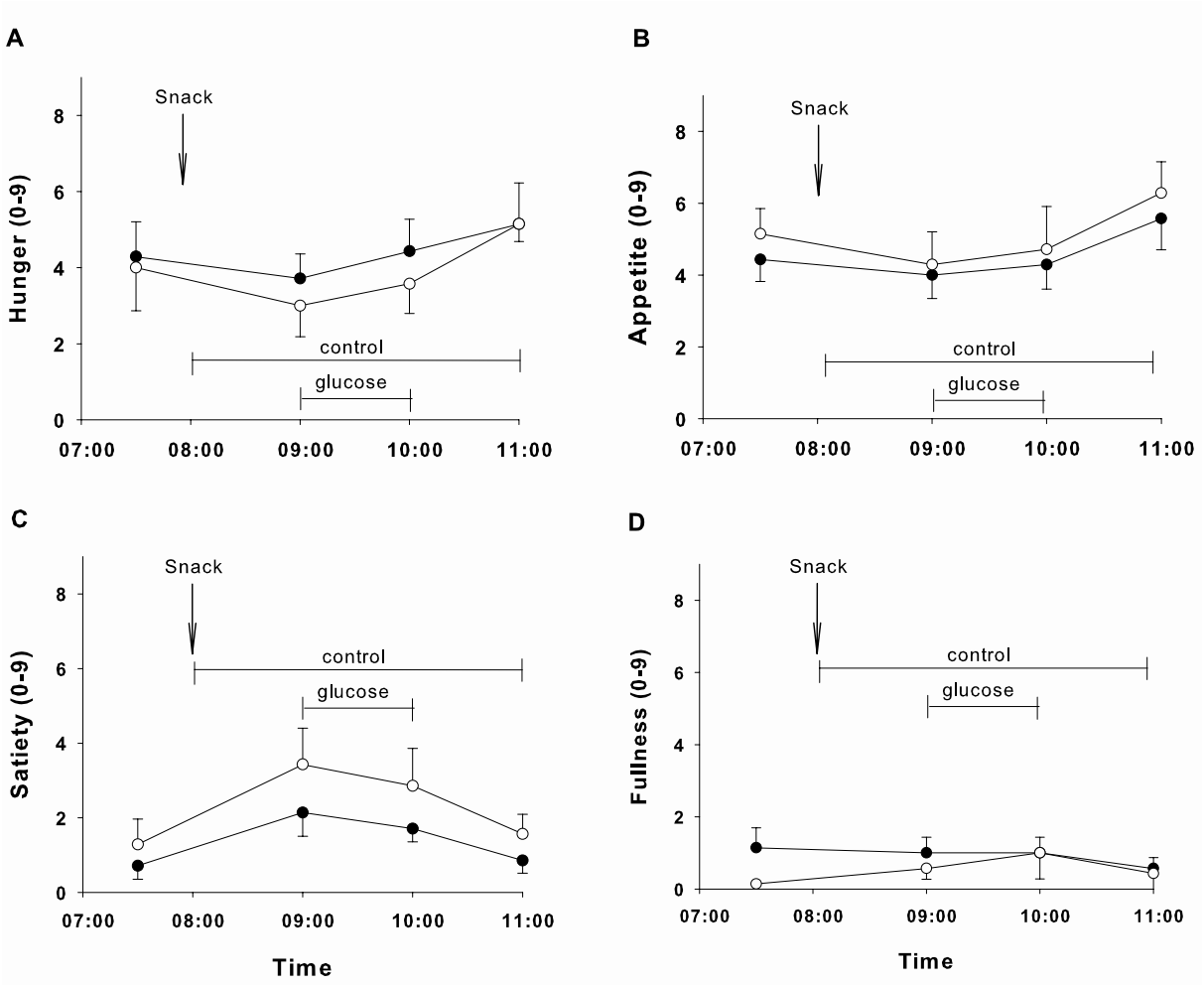

Figure 2: Mean (± SEM) scores of self-rated feelings of (A) hunger, (B) appetite, (C) satiety, and (D) fullness during a total period of 270 minutes with either a 60 min infusion of 500 ml 10% glucose solution (black circles) or a continuous infusion of 500 ml 0.9% NaCl (open circles). The arrow indicates ingestion of the breakfast snack at 08:00 h while horizontal lines indicate the periods of respective infusions.

Discussion

To the best of our knowledge this study is the first to induce dynamic fluctuations in glycaemia in humans by intravenous glucose infusion while concurrently assessing subjective feelings of hunger, appetite, satiety, and fullness. In contrast to our hypothesis, fluctuations of blood glucose and insulin that were comparable to those after regular meals failed to affect hunger, appetite, satiety or fullness ratings in young healthy men. These findings challenge the common notion of circulating glucose and insulin levels playing a prominent role in the short-term regulation of hunger, appetite, and satiety after a light meal.

Noteworthy, the end of the glucose infusion in our study was followed by a sharp fall in blood glucose concentrations reaching a mild hypoglycemic nadir level of ~3.0 mmol/l. Most (Schultes et al., 2005a; Schultes et al., 2003) but not all (Schultes, Schmid, Wilms, Jauch-Chara, Oltmanns, & Hallschmid, 2012) hypoglycemic clamp studies have found that blood glucose levels of 3.0 mmol/l increase feelings of hunger which was obviously not the case here. Considering that blood glucose levels in previous hypoglycemic clamp studies persisted over a longer time (about 45 min) within the hypoglycemic range, it is reasonably to assume that the rather short reactive hypoglycemia following the glucose infusion was not a signal strong enough to stimulate hunger.

Our findings might also challenge the popular concept of low glycemic index diets to lose body weight. Advocates of this dietary approach often argue that large glycemic (and concurrent insulinemic) fluctuations induced by the intake of high glycemic index foods can trigger feelings of hunger and, thus, on the long run favor weight gain (Roberts, 2003). Our results argue against this notion since the sharp drop in circulating glucose after the end of the glucose infusion remained without effect on hunger ratings, at least within the time period covered by our experiment. Of note in this context, several clinical dietary intervention trials (Papadaki et al., 2014; Sichieri, Moura, Genelhu, Hu, & Willett, 2007; Sloth et al., 2004) have failed to show an advantage of low glycemic index dietary approaches for weight loss in overweight/obese subjects in comparison with other dietary approaches.

Several limitations of our study need to be mentioned. First, we did not assess actual food intake. Previous studies (Beglinger, & Degen, 2006; Benedict et al., 2008; Chapman et al., 1998) have shown that changes in voluntary food intake upon experimental manipulation can occur even without subjective changes in hunger, appetite, satiety, and fullness. Second, we cannot exclude a modulating influence of circulating glucose levels on the regulatory effects of other food-related appetite signals. For instance, a previous experimental study (Lam, Gielkens, de Boer, Lamers, & Masclee, 1998) has shown that hyperglycemia as compared to euglycemia can even reverse the satiating effects of CCK, an effect that is believed to be mediated by a hyperglycemia-induced reduction of the vagal-cholinergic system activity. Also, hyperglycemia has been well documented to modulate pyloric motility during intraduodenal lipid infusion, i.e. an effect that was also associated with reduced perception of hunger feelings (Andrews et al., 1998). Third, we used a numeric rating scale to assess appetite-related symptoms that was, in contrast to the more commonly used visual analog scale (VAS) (Flint, Raben, Blundell, & Astrup, 2000) not formally validated. However, to the best of our knowledge there is no evidence to assume that the use of a VAS would have yield substantially different results. A further limitation is that the study was performed in an only single blind-design. Lastly, since our study only included male subjects our results cannot necessarily be generalized to women.

In conclusion, our findings challenge the hypothesis that glucose and insulin levels play a prominent role in the regulation of hunger, appetite, and satiety after a light meal."

Acknowledgments

Supported by grants from the German Federal Ministry of Education and Research (BMBF) to the German Center for Diabetes Research (DZD e.V.; 01GI0925), and the Deutsche Forschungsgemeinschaft (DFG) KFO-126.

References

Adachi, A., Shimizu, N., Oomura, Y., & Kobáshi, M. (1984). Convergence of hepatoportal glucose-sensitive afferent signals to glucose-sensitive units within the nucleus of the solitary tract. *Neuroscience Letters*, *46*(2), 215–218.

Andrews, J. M., Rayner, C. K., Doran, S., Hebbard, G. S., & Horowitz, M. (1998). Physiological changes in blood glucose affect appetite and pyloric motility during intraduodenal lipid infusion. *The American Journal of Physiology*, *275*(4 Pt 1), G797–804.

Beglinger, C., & Degen, L. (2006). Gastrointestinal satiety signals in humans--physiologic roles for GLP-1 and PYY? *Physiology & Behavior*, *89*(4), 460–464.

Benedict, C., Kern, W., Schultes, B., Born, J., & Hallschmid, M. (2008). Differential sensitivity of men and women to anorexigenic and memory-improving effects of intranasal insulin. *The Journal of Clinical Endocrinology and Metabolism*, *93*(4), 1339–1344.

Born, J., Lange, T., Kern, W., McGregor, G. P., Bickel, U., & Fehm, H. L. (2002). Sniffing neuropeptides: a transnasal approach to the human brain. *Nature Neuroscience*, *5*(6), 514–516.

Brody, S., Keller, U., Degen, L., Cox, D. J., & Schächinger, H. (2004). Selective processing of food words during insulin-induced hypoglycemia in healthy humans. *Psychopharmacology*, *173*(1-2), 217–220.

Burdakov, D., Luckman, S. M., & Verkhratsky, A. (2005). Glucose-sensing neurons of the hypothalamus. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *360*(1464), 2227–2235.

Chapman, I. M., Goble, E. A., Wittert, G. A., Morley, J. E., & Horowitz, M. (1998). Effect of intravenous glucose and euglycemic insulin infusions on short-term appetite and food intake. *The American Journal of Physiology*, *274*(3 Pt 2), R596–603.

Dunn-Meynell, A. A., Sanders, N. M., Compton, D., Becker, T. C., Eiki, J., Zhang, B. B., & Levin, B. E. (2009). Relationship among brain and blood glucose levels and spontaneous and glucoprivic feeding. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *29*(21), 7015–7022.

Flint, A., Gregersen, N. T., Gluud, L. L., Møller, B. K., Raben, A., Tetens, I., Verdich, C., & Astrup, A. (2007). Associations between postprandial insulin and blood glucose responses, appetite sensations and energy intake in normal weight and overweight individuals: a meta-analysis of test meal studies. *The British Journal of Nutrition*,

98(1), 17–25.

Flint, A., Møller, B. K., Raben, A., Sloth, B., Pedersen, D., Tetens, I., Holst, J. J., Astrup, A. (2006). Glycemic and insulinemic responses as determinants of appetite in humans. *The American Journal of Clinical Nutrition*, *84*(6), 1365–1373.

Flint, A., Raben, A., Blundell, J. E., & Astrup, A. (2000). Reproducibility, power and validity of visual analogue scales in assessment of appetite sensations in single test meal studies. *International Journal of Obesity and Related Metabolic Disorders: Journal of the International Association for the Study of Obesity*, *24*(1), 38–48.

Fruehwald-Schultes, B., Kern, W., Oltmanns, K. M., Sopke, S., Toschek, B., Born, J., Fehm, H. L., & Peters, A. (2001). Metformin does not adversely affect hormonal and symptomatic responses to recurrent hypoglycemia. *The Journal of Clinical Endocrinology and Metabolism*, *86*(9), 4187–4192.

Gielkens, H. A., Verkijk, M., Lam, W. F., Lamers, C. B., & Masclee, A. A. (1998). Effects of hyperglycemia and hyperinsulinemia on satiety in humans. *Metabolism: Clinical and Experimental*, *47*(3), 321–324.

Hallschmid, M., Higgs, S., Thienel, M., Ott, V., & Lehnert, H. (2012). Postprandial administration of intranasal insulin intensifies satiety and reduces intake of palatable snacks in women. *Diabetes*, *61*(4), 782–789.

Hevener, A. L., Bergman, R. N., & Donovan, C. M. (2001). Hypoglycemic detection does not occur in the hepatic artery or liver: findings consistent with a portal vein glucosensor locus. *Diabetes*, *50*(2), 399–403.

Karnani, M., & Burdakov, D. (2011). Multiple hypothalamic circuits sense and regulate glucose levels. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, *300*(1), R47–55. http://doi.org/10.1152/ajpregu.00527.2010

Lam, W. F., Gielkens, H. A., de Boer, S. Y., Lamers, C. B., & Masclee, A. A. (1998). Influence of hyperglycemia on the satiating effect of CCK in humans. *Physiology & Behavior*, *65*(3), 505–511.

Lavin, J. H., Wittert, G., Sun, W. M., Horowitz, M., Morley, J. E., & Read, N. W. (1996). Appetite regulation by carbohydrate: role of blood glucose and gastrointestinal hormones. *The American Journal of Physiology*, *271*(2 Pt 1), E209–214.

Levin, B. E. (2007). Neuronal glucose sensing: still a physiological orphan? *Cell Metabolism*, *6*(4), 252–254. http://doi.org/10.1016/j.cmet.2007.09.005

Levin, B. E., Routh, V. H., Kang, L., Sanders, N. M., & Dunn-Meynell, A. A. (2004). Neuronal glucosensing: what do we know after 50 years? *Diabetes*, *53*(10), 2521–

2528.

Liu, M., Seino, S., & Kirchgessner, A. L. (1999). Identification and characterization of glucoresponsive neurons in the enteric nervous system. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *19*(23), 10305–10317.

Mayer, J. (1952). The glucostatic theory of regulation of food intake and the problem of obesity. *Bulletin. New England Medical Center*, *14*(2), 43–49.

Melanson, K. J., Westerterp-Plantenga, M. S., Saris, W. H., Smith, F. J., & Campfield, L. A. (1999). Blood glucose patterns and appetite in time-blinded humans: carbohydrate versus fat. *The American Journal of Physiology*, *277*(2 Pt 2), R337–345.

Morton, G. J., Meek, T. H., & Schwartz, M. W. (2014). Neurobiology of food intake in health and disease. *Nature Reviews. Neuroscience*, *15*(6), 367–378.

Papadaki, A., Linardakis, M., Plada, M., Larsen, T. M., Damsgaard, C. T., van Baak, M. A., Jebb, S., Pfeiffer, A. F. H., Martinez, J. A., Handjieva-Darlenska, T., Kunesova, M., Holst, C., Saris, W. H. M., Astrup, A., & Kafatos, A. (2014). Impact of weight loss and maintenance with ad libitum diets varying in protein and glycemic index content on metabolic syndrome. *Nutrition (Burbank, Los Angeles County, Calif.)*, *30*(4), 410–417.

Pardal, R., & López-Barneo, J. (2002). Low glucose-sensing cells in the carotid body. *Nature Neuroscience*, *5*(3), 197–198.

Ritter, S., Dinh, T. T., & Zhang, Y. (2000). Localization of hindbrain glucoreceptive sites controlling food intake and blood glucose. *Brain Research*, *856*(1-2), 37–47.

Roberts, S. B. (2003). Glycemic index and satiety. *Nutrition in Clinical Care: An Official Publication of Tufts University*, *6*(1), 20–26.

Schmid, S. M., Hallschmid, M., Jauch-Chara, K., Bandorf, N., Born, J., & Schultes, B. (2007). Sleep loss alters basal metabolic hormone secretion and modulates the dynamic counterregulatory response to hypoglycemia. *The Journal of Clinical Endocrinology and Metabolism*, *92*(8), 3044–3051.

Schmid, S. M., Jauch-Chara, K., Hallschmid, M., Oltmanns, K. M., Born, J., & Schultes, B. (2008). Short-term nocturnal hypoglycaemia increases morning food intake in healthy humans. *Diabetic Medicine: A Journal of the British Diabetic Association*, *25*(2), 232–235.

Schultes, B., Schmid, S. M., Wilms, B., Jauch-Chara, K., Oltmanns, K. M., & Hallschmid, M. (2012). Lactate infusion during euglycemia but not hypoglycemia reduces subsequent food intake in healthy men. *Appetite*, *58*(3), 818–821.

Schultes, B., Kern, W., Oltmanns, K., Peters, A., Gais, S., Fehm, H. L., & Born, J. (2005a). Differential adaptation of neurocognitive brain functions to recurrent hypoglycemia in healthy men. *Psychoneuroendocrinology*, *30*(2), 149–161.

Schultes, B., Peters, A., Kern, W., Gais, S., Oltmanns, K. M., Fehm, H. L., & Born, J. (2005b). Processing of food stimuli is selectively enhanced during insulin-induced hypoglycemia in healthy men. *Psychoneuroendocrinology*, *30*(5), 496–504.

Schultes, B., Peters, A., Hallschmid, M., Benedict, C., Merl, V., Oltmanns, K. M., Born, J., Fehm, H. L., & Kern, W. (2005c). Modulation of food intake by glucose in patients with type 2 diabetes. *Diabetes Care*, *28*(12), 2884–2889.

Schultes, B., Oltmanns, K. M., Kern, W., Fehm, H. L., Born, J., & Peters, A. (2003). Modulation of hunger by plasma glucose and metformin. *The Journal of Clinical Endocrinology and Metabolism*, *88*(3), 1133–1141.

Sichieri, R., Moura, A. S., Genelhu, V., Hu, F., & Willett, W. C. (2007). An 18-mo randomized trial of a low-glycemic-index diet and weight change in Brazilian women. *The American Journal of Clinical Nutrition*, *86*(3), 707–713.

Sloth, B., Krog-Mikkelsen, I., Flint, A., Tetens, I., Björck, I., Vinoy, S., Elmstahl, H., Astrup, A., Lang, V., & Raben, A. (2004). No difference in body weight decrease between a low-glycemic-index and a high-glycemic-index diet but reduced LDL cholesterol after 10-wk ad libitum intake of the low-glycemic-index diet. *The American Journal of Clinical Nutrition*, *80*(2), 337–347.

Stunkard, A. J., & Messick, S. (1985). The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. *Journal of Psychosomatic Research*, *29*(1), 71–83.

Woods, S. C., Lutz, T. A., Geary, N., & Langhans, W. (2006). Pancreatic signals controlling food intake; insulin, glucagon and amylin. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *361*(1471), 1219–1235.