Published in final edited form as:

Int J Obes (Lond). 2011 December ; 35(12): 1495–1501. doi:10.1038/ijo.2011.13.

Higher incremental insulin area under the curve during oral glucose tolerance test predicts less food intake and weight gain

J He, S Votruba, C Venti, and J Krakoff

Department of Health and Human Services, Phoenix Epidemiology and Clinical Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Phoenix, AZ, USA

Abstract

Objective: To investigate the correlation of peripheral insulin concentrations with food intake and body weight.

Design: Cross sectional and longitudinal clinical study: we investigated the association of peripheral insulin concentrations in response to an oral glucose tolerance test (OGTT) with subsequent measures of *ad libitum* food intake and body weight change.

Subjects: Food intake analysis: Pima Indians ($n = 67$, 63% male; body mass index (mean $\pm$ s.d.) 34.2 ± 9.4 kg m $^{-2}$) with normal glucose regulation (NGR; fasting glucose <5.6 mmol l $^{-1}$ and 2-h glucose <7.8 mmol l $^{-1}$) participated in a study of *ad libitum* food intake measured over 3 days by an automated vending machine system. Weight change analysis: Pima Indians with NGR ($n = 339$) who also participated in a longitudinal study of risks for type 2 diabetes and had follow-up weights.

Results: Food intake analysis: incremental area under the curve (iAUC) for insulin during the OGTT was negatively associated with mean daily *ad libitum* energy intake (DEI) ($r = -0.26$, $P = 0.04$), calories consumed as percent weight-maintenance energy needs (%WMEN) ($r = -0.38$, $P = 0.002$) and carbohydrate intake (gram per day) ($r = -0.35$, $P = 0.005$). Adjustment for age and sex attenuated the association of iAUC with DEI ($P = 0.06$) not with %WMEN and carbohydrate intake ($P = 0.005$, $P = 0.008$). Weight change analysis: after adjustment for age, sex, follow-up time and initial body weight, higher insulin iAUC predicted less absolute and percent weight change ($\beta = -6.9$, $P = 0.02$; $\beta = -0.08$, $P = 0.008$, respectively).

Conclusions: In healthy Pima Indians with NGR, higher plasma iAUC during an OGTT predicted lower food intake and carbohydrate consumption and less weight gain. These data indicated a role for peripheral insulin as a negative feedback signal in the regulation of energy intake and body weight.

Keywords

insulin; food intake; weight gain; subjects with normal glucose regulation

Correspondence: Dr J He, Phoenix Epidemiology and Clinical Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 4212 N 16th St, Rm 5-35, Phoenix, AZ 85016, USA. hejianying@mail.nih.gov.

Conflict of interest

The authors declare no conflict of interest.

Introduction

Increased adiposity is a significant public health problem and leads to a myriad of health problems. Weight gain is a result of an imbalance between energy intake and energy expenditure. In our current food rich environment understanding factors which might influence food intake are important. Regulation of eating behavior involves central integration of peripherally derived signals that affect satiation and satiety. Insulin is one such peripheral signal which may work centrally to terminate food intake.

It has been known for some time that intra-cerebral injection of insulin in rats and baboons decreased food intake¹⁻³ and body weight.^{1,3} In these animals, central insulin administration increased melanocortin and decreased neuropeptide Y signaling thus having a role in the control of energy balance.⁴⁻⁶ Whether peripheral insulin acts as a central signal in regulating caloric intake in humans is not yet clear. Cerebrospinal fluid (central) insulin concentrations do appear to be lower in obese individuals compared with lean.⁷ It has also been observed that peripheral (skeletal muscle) insulin resistance and higher fasting plasma insulin concentrations are associated with lower rates of weight gain in adult Pima Indians⁸ and other populations.⁹ More directly supportive of an important CNS effect of insulin on energy balance is the finding that nasally administered insulin reduced adiposity in men over 8 weeks.¹⁰

Given this evidence, we investigated whether insulin area under the curve (AUC) during an oral glucose tolerance test (OGTT) in Pima Indians with normal glucose regulation (NGR) was associated with subsequent *ad libitum* energy intake from a highly reproducible automated food-selection system¹¹⁻¹³ and, in a separate analysis, follow-up changes in body weight.

Subjects and methods

Subjects

Food intake analysis.—To assess the effect of peripheral insulin response on food intake, adult Native Americans ($n = 67$, 45 men and 22 women) at least one-half Pima or closely related Tohono O'odham Indians participated in an ongoing study investigating a variety of factors, which may affect *ad libitum* energy intake. To minimize the effect of altered glucose homeostasis on insulin concentrations, only those with NGR (fasting plasma glucose <5.6 mmol l⁻¹ and 2-h plasma glucose <7.8 mmol l⁻¹) as assessed by 75-g oral glucose tolerance testing were included.¹⁴

All volunteers were found to be free of disease according to physical examinations, medical histories and laboratory tests. All volunteers were initially admitted to the Clinical Research Unit of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in Phoenix, AZ, USA for 8–15 days. Follow-up weights and OGTT results were obtained from volunteers who had follow-up admissions to the clinical research unit or who also participated in an outpatient study of risk factors for type 2 diabetes. The studies were

approved by the NIDDK Institutional Review Board. Before participation, written informed consent was obtained at each visit.

Weight change analysis.—Members of the Gila River (Pima) Indian Community also participated in longitudinal studies of risk factors for type 2 diabetes and obesity. To determine the relationship between peripheral insulin response and weight gain, 339 adults (at least one-half Pima or closely related Tohono O’odham Indians; 214 men and 125 women) with a baseline OGTT with insulin measured at multiple time points (see Methods below) and who were NGR at both the baseline and with a follow-up visit (mean follow-up time 8.5 ± 6.0 years), with a recorded follow-up weight at least 6 months after the initial visit were included.

Methods

Food intake analysis.—On admission volunteers were started on a standard weight-maintaining diet (20% protein, 30% fat and 50% carbohydrate) for 3 days. Height was measured using a stadiometer; weight was measured using an electronic digital scale. Weight-maintenance energy needs (WMEN) specific to the inpatient unit were calculated based on body weight and sex: WMEN for men: $9.5 \times \text{weight (kg)} + 1973$; for women, WMEN: $9.5 \times \text{weight (kg)} + 1745$.¹⁵ On the second day after admission, body composition was assessed by using dual energy X-ray absorptiometry (Lunar Corp., Madison, WI, USA), and percentage body fat (%BF), fat mass and fat-free mass were calculated as previously described.¹⁵ On day 4 after admission, a 75-g OGTT was performed with insulin and glucose concentrations measured at −15, 0, 30, 60, 120 and 180 min. For the food intake evaluation, the use of the automated vending machines has been previously described.^{11–13} In brief, the foodstuffs made available to the volunteers in the automated food-vending system were based on a food preference questionnaire.¹⁶ For each day on the vending system, the same 8 breakfast items, 22 lunch or dinner items and 10 snack items were provided to the volunteer. In addition, a core group of condiments, juice and soda were provided each day. Each volunteer was assigned to a single, refrigerated vending machine and had access to the machine for 23.5 h each day. Volunteers were required to eat in a separate dining area that had no television. Food selection was monitored by the computerized vending system, and food wrappers and unconsumed food were returned to the metabolic kitchen to be weighed. Energy and macronutrient intakes during the *ad libitum* feeding period were calculated from the Food Processor Professional Diet Analyzer Program (ESHA version 10.0.0, ESHA Research, Salem, OR, USA) as previously described.¹⁷ Volunteers began consuming from the computerized vending machine system after at least 6 days of consuming the weight-maintaining diet. All volunteers spent 3 days in selecting foods from the vending machine system and results are presented as the mean daily energy intake (DEI) over that period. Percent WMEN (%WMEN) was calculated by $\text{DEI}/\text{WMEN} \times 100$.

Weight change analysis.—Volunteers were admitted to the clinical research unit and fed a weight-maintaining diet, and OGTT performed as described above. Weight at follow-up was determined by follow-up admission to the clinical research unit or outpatient visit during which an OGTT was available demonstrating the volunteer remained NGR. Changes

of body weight were expressed as absolute weight change (kg) (final weight–initial weight) or the percent weight change ((final weight–initial weight)/(initial weight× 100%)).

Plasma glucose concentration was determined by the glucose oxidase method (Beckman Instruments, Fullerton, CA, USA). Plasma insulin concentrations were measured by the Herbert modification of the method of Yalow and Berson¹⁸ by an automated auto-analyzer (ICN Radiochemicals Inc., Costa Mesa, CA, USA) or by an automated immunoassay (Access, Beckman Instruments). Values from the final two assays were regressed to the original assay. Incremental insulin area under the curve (iAUC) and incremental glucose area under the curve (gAUC) were calculated using the trapezoidal method.

Statistical analysis—Statistical analyses were performed using SAS software (SAS version 9.1, SAS Institute, Inc., Cary, NC, USA). Normality of the data was tested by the Shapiro-Wilk test. Non-normally distributed variables were log transformed to approximate normal distributions. If normal distribution was not achieved by logarithmic transformation, non-parametric tests were used. Student's *t*-test or Wilcoxon test was used for sex comparisons for continuous variables. Pearson correlation analysis was used to test the relationships between variables. The effect of confounders was accounted for by general linear models. For the prospective analysis, a general linear model was used to test associations of baseline iAUC with changes in weight adjusted for covariates. Level of statistical significance was set at $P<0.05$.

Results

Subject characteristics

Subject anthropometric, caloric intake and body weight change variables from both groups are shown in Table 1. As previously reported,¹⁷ volunteers routinely overate during the *ad libitum* food intake study. Subjects in the weight gain analysis group were slightly younger and weighed less at the start than the subjects in the food intake study. For the weight change analysis, body weight increased by a mean of 7.6 (–44 to –64) kg over a follow-up time of 8.5 (0.6–25) years.

Correlation of food intake with age and anthropometric variables

Age was not associated with total energy or any of the specific macronutrient intakes. DEI was negatively associated with %BF ($r = -0.34$, $P < 0.01$) and mean daily carbohydrate intake was negatively associated with body mass index ($r = -0.26$, $P = 0.03$) and %BF ($r = -0.34$, $P < 0.01$). However, the negative association between DEI and %BF was due to a sex effect, as women had higher %BF but ate less than men. After adjustment for sex, the association between %BF and DEI was no longer significant (Table 2), but the association between carbohydrate intake and %BF remained significant ($r = -0.27$, $P = 0.03$).

Correlations between DEI, %WMEN, carbohydrate intake and insulin concentrations

Incremental iAUC was negatively associated with DEI, %WMEN and mean daily carbohydrate intake ($r = -0.26$, $P = 0.04$; $r = -0.38$, $P = 0.002$; $r = -0.35$, $P = 0.005$, respectively) (Figures 1A–C). In models adjusted for age and sex, the association of iAUC

with DEI was slightly attenuated ($\beta = -942$, $P = 0.06$), but the associations with %WMEN and carbohydrate intake ($\beta = -0.55$, $P = 0.005$; $\beta = -161.4$, $P = 0.008$) remained significant. Except in the specific case of carbohydrate intake, %BF was not a determinant of food intake independent of sex. As expected %BF was strongly associated with iAUC ($r = 0.47$, $P = 0.0001$). Addition of %BF to the models attenuated the association of iAUC with DEI, %WMEN and carbohydrate intake ($P = 0.06$, $P = 0.09$ and $P = 0.06$, respectively) but was not itself a predictor in any of the models. gAUC was also correlated with DEI ($r = -0.27$, $P = 0.03$), %WMEN ($r = -0.32$, $P = 0.008$) and mean daily carbohydrate intake ($r = -0.3$, $P = 0.02$). gAUC was not a predictor of any of the energy intake variables in the models with iAUC, but slightly modified the association of iAUC with %WMEN and carbohydrate intake ($P = 0.07$ and $P = 0.06$, respectively).

Correlation analysis of iAUC with changes in body weight

The absolute weight change and percent weight change were negatively associated with iAUC ($r = -0.16$, $P = 0.003$; $r = -0.23$, $P < 0.0001$, respectively) (Figures 2A and B). After adjustment for age, sex, follow-up time and baseline body weight, the associations of iAUC with absolute weight change ($\beta = -6.9$, $P = 0.02$) and percent weight change remained significant ($\beta = -0.08$, $P = 0.008$) (Table 3). In models including gAUC, gAUC was a predictor of weight gain, but iAUC was no longer significant.

Discussion

In this study, in Pima Indians with NGR, we found a negative correlation between incremental insulin AUC during an OGTT and *ad libitum* food intake as measured by mean total DEI, %WMEN and carbohydrate intake on an inpatient unit using a reproducible automated vending machine system. Despite differences in caloric intake in this system by sex, adjustment for age and sex attenuated the association with DEI, but those with %WMEN and carbohydrate intake remained highly significant. In support of these findings, we also found that iAUC was negatively correlated with weight change in a larger, prospective analysis.

These findings indicate that postprandial increases in peripheral plasma insulin concentrations may serve as a short-term satiety signal and prompt termination of food consumption. The mechanism of how peripheral insulin would induce satiety is unclear, but would presumably be via a CNS effect. Insulin has been shown to be a negative regulator of food intake and body weight in animals when administered directly into the CNS. Chronic infusion of insulin into the CNS decreased food intake and body weight in rats¹⁹ and baboons,^{1,3} while central administration of insulin antibodies is associated with an increase in food intake in rats.² Lower cerebrospinal fluid insulin concentrations lead to increased food consumption and an increase in body weight in rodents over time.²⁰ Recently, a human study demonstrated that intra-nasal insulin reduced body fat in men.¹⁰ In this latter study, energy expenditure, as measured by resting metabolic rate, was not altered thus it is reasonable to hypothesize that reduced food intake accounted for the observed weight loss.

The effect of peripheral insulin on food intake was also examined in animals, as published, rats receiving chronic peripheral injections of low dose insulin at meals when hypoglycemia

was avoided tended to consume smaller amounts at each meal.^{21,22} In humans given serial test meals with differing macronutrient content after which *ad libitum* food intake was measured, those meals which produced a higher insulin AUC resulted in lower subsequent *ad libitum* food intake.²³ The negative correlation between iAUC and food intake in our study would assume a peripheral effect of insulin may act through CNS by crossing blood–brain barrier, because central insulin and peripheral insulin are highly correlated in animals,²⁴ and there is additional evidence of reduced transport of insulin to the brain in obese animals.²⁵ Interestingly, insulin transport from plasma into the CNS is inhibited by dexamethasone, which could explain the orexogenic effects of glucocorticoids on food intake.^{26,27} Direct data on the association and effect of peripheral and central insulin concentrations in humans are scant, but it was found that obese individuals may in fact have lower insulin levels than lean individuals.⁷

We did not have measures of CNS insulin concentrations, because it was impractical to do in healthy humans. But, as peripheral insulin concentrations are estimated to take ~60–90 min to cross the blood–brain barrier²⁸ and peak insulin concentrations during the OGTT occurred at an average of 45 ± 15 min following the glucose load in our study, the 120-min time point seemed to be the approximate time of peak insulin time plus blood–brain barrier crossing time. Thus, it may be that the 120-min insulin concentrations is representative of the sustained CNS levels and explains why this time point is associated with lower DEI, %WMEN and carbohydrate intake ($r = -0.33$, $P = 0.007$; $r = -0.42$, $P = 0.0004$; $r = -0.38$, $P = 0.002$, respectively), as well as the difference between 120-min insulin concentration and fasting insulin concentration following OGTT ($r = -0.35$, $P = 0.005$; $r = -0.41$, $P = 0.0008$; $r = -0.36$, $P = 0.004$, respectively), rather than any other time point of insulin concentration during OGTT including peak insulin with food intake (data not shown). This may indicate that fluctuations in insulin concentrations are important in regulating energy intake.

It is possible that peripheral insulin affects food intake by other mechanisms independent of a direct central effect. For instance, insulin inhibits production of ghrelin²⁹ which may promote food intake, and enhance the sensitivity of neurons to the satiety signal cholecystikinin (CCK).³⁰ But to identify the effect of gastrointestinal hormones on food intake will be a different study, and needs further investigation, and our study focused on the link between insulin from OGTT and food intake. Alternatively, perhaps the peripheral insulin concentrations are affecting glycogen stores. Hepatic glycogenolysis is sensitive to relatively small changes in insulin concentrations.³¹ The amount of stored glycogen has been implicated in subsequent energy intake.³² Thus, relatively higher insulin concentrations promoting greater hepatic glycogen stores may be a potential mechanism by which peripheral insulinemia affects food intake. It is interesting that we found an even stronger association between carbohydrate ingestion and insulin concentrations. As carbohydrate ingestion would replete glycogen preferentially, this may be further indication of the insulin–glycogen affect.

Leptin may also have an important role in food intake and weight gain. Leptin concentrations were not available for weight change group. We had leptin concentrations measured in food intake group. We did not find any association between fasting leptin and %WMEN, mean of DEI or mean of carbohydrate intake (data not shown). Leptin and insulin

have separate signaling pathways. Thus, the effect of iAUC on food intake and weight gain could be independent of leptin or leptin resistance.

The negative association between body weight gain and iAUC supports our observation of the negative association between iAUC and food intake. It should be noted that the associations with food intake and weight gain were only found in individuals with NGR. When individuals with impaired glucose regulation or diabetes were included the associations were not significant (data not shown). The defect in insulin action and secretion that accompany impaired glucose regulation and diabetes may alter any effect of insulin on satiety. It is generally accepted that insulin concentrations are inversely correlated with insulin sensitivity. In the weight change analysis, in those individuals who also had measurements of insulin action using the euglycemic-hyperinsulinemic clamp technique (M), there was a strong inverse correlation between M and iAUC ($r = -0.68$, $P < 0.0001$). No clamp measures were available in the food intake analysis, but as expected, insulin sensitivity calculated as Matsuda index was also highly inversely correlated with iAUC ($r = -0.87$, $P < 0.0001$). Therefore, high iAUC could be considered a surrogate of insulin resistance. Greater insulin sensitivity does predict greater weight gain in a previous study in Pima Indians. In our current study, adding M-low to the models attenuated the effect of iAUC on weight change (data not shown). However, adding the calculated Matsuda index did not alter the significant association of iAUC with %WMEN, mean DEI or mean daily carbohydrate intake (data not shown).

Incremental gAUC was correlated with %WMEN, mean DEI and mean daily carbohydrate intake, however, once iAUC was added to the models, gAUC was not a predictor of any of the measures of food intake. Nor was rapid decline in glucose (change from peak to 180 min glucose) associated with food intake measures (data not shown).

It should be noted that in those with NGR the association between weight change and iAUC did not remain significant after taking gAUC or insulin sensitivity into account. This may indicate that peripheral insulin concentrations act more directly as a short-term satiety signal, but that the effect may not be as apparent over the longer term when other peripheral signals may influence energy balance.

One might argue that subjects with smaller body size may have had a higher insulin response in contrast to those with a larger body size when challenged with the same amount of glucose during the OGTT, that is, 75 g of glucose, explaining the association of iAUC with food intake and weight gain. However, body weight was, if anything, negatively associated with energy intake, which was primarily an effect of sex. In addition, initial weight was not associated with iAUC. Thus, we do not believe that this confounded our observations. Although not associated, the degree of hyperinsulinemia may be due in part to body weight and sex, in the weight change analysis, initial body weight and gender were included as confounders in the general linear model, and iAUC significantly predicted weight gain independent of these parameters. Replacing initial body weight with body mass index did not change the results. There was no interaction between sex and iAUC nor did analyzing men and women separately change the results. Finally, as shown in Table 3, age was negatively associated with weight gain. This may reflect greater potential for weight gain in

younger individuals. However, despite iAUC remained independent of age in the models. Less weight gain with age in our study may indicate the involvement of aging-related factors.

It must be acknowledged that our results were found in Pima Indians, a population with high rates of obesity and type 2 diabetes, so generalizability to other populations is unknown. Moreover, although our vending machine paradigm is a highly reproducible measurement of food intake,¹⁷ it is not representative of ‘real world’ food intake. In addition, we note that the association was attenuated with addition of body fat to the models. However, as noted since iAUC and %BF are highly correlated, and since %BF is not a determinant of energy intake, the attenuated association of iAUC was likely due to the shared variance in the model with the addition of %BF.

In conclusion, in Pima Indians with NGR, higher plasma iAUC in response to OGTT predicted lower food consumption and less weight gain. These results indicate a physiologic role for insulin as a negative feedback signal in the short-term regulation of food intake and possibly long term control of weight gain.

Acknowledgements

We thank the dietary, nursing and technical staff of the Clinical Research Unit of the National Institute of Diabetes, Digestive and Kidney Disease in Phoenix, AZ for their assistance. Most of all, we thank the volunteers for their participation in the study. The authors responsibilities were as follows—SBV and JK: study design; JYH: menu planning; JYH and CAV: data collection; JYH and JK: data analysis; JYH, SBV and JK: study manuscript composition; JYH: manuscript preparation. All authors helped to prepare the manuscript for submission. Funding for the study was via the NIDDK intra-mural research program. This study was supported by the Intramural Research Program of the NIH, NIDDK.

References

1. Porte D, Jr, Woods SC. Regulation of food intake and body weight in insulin. *Diabetologia* 1981; 20 (Suppl): 274–280.
2. Strubbe JH, Mein CG. Increased feeding in response to bilateral injection of insulin antibodies in the VMH. *Physiol Behav* 1977; 19: 309–313. [PubMed: 607241]
3. Woods SC, Lotter EC, McKay LD, Porte D, Jr. Chronic intracerebroventricular infusion of insulin reduces food intake and body weight of baboons. *Nature* 1979; 282: 503–505. [PubMed: 116135]
4. Benoit SC, Air EL, Coolen LM, Strauss R, Jackman A, Clegg DJ et al. The catabolic action of insulin in the brain is mediated by melanocortins. *J Neurosci* 2002; 22: 9048–9052. [PubMed: 12388611]
5. Mayer CM, Belsham DD. Insulin directly regulates NPY and AgRP gene expression via the MAPK MEK/ERK signal transduction pathway in mHypoE-46 hypothalamic neurons. *Mol Cell Endocrinol* 2009; 307: 99–108. [PubMed: 19524132]
6. Schwartz MW, Sipols AJ, Marks JL, Sanacora G, White JD, Scheurink A et al. Inhibition of hypothalamic neuropeptide Y gene expression by insulin. *Endocrinology* 1992; 130: 3608–3616. [PubMed: 1597158]
7. Kern W Reduced transport of insulin across the blood/brain barrier in obese humans. *Diabetes* 2003; (Suppl) A559.
8. Swinburn BA, Nyomba BL, Saad MF, Zurlo F, Raz I, Knowler WC et al. Insulin resistance associated with lower rates of weight gain in Pima Indians. *J Clin Invest* 1991; 88: 168–173. [PubMed: 2056116]

9. Wedick NM, Mayer-Davis EJ, Wingard DL, Addy CL, Barrett-Connor E. Insulin resistance precedes weight loss in adults without diabetes: the Rancho Bernardo Study. *Am J Epidemiol* 2001; 153: 1199–1205. [PubMed: 11415955]
10. Hallschmid M, Benedict C, Schultes B, Fehm HL, Born J, Kern W. Intranasal insulin reduces body fat in men but not in women. *Diabetes* 2004; 53: 3024–3029. [PubMed: 15504987]
11. Larson DE, Rising R, Ferraro RT, Ravussin E. Spontaneous overfeeding with a ‘cafeteria diet’ in men: effects on 24-h energy expenditure and substrate oxidation. *Int J Obes Relat Metab Disord* 1995; 19: 331–337. [PubMed: 7647825]
12. Rising R, Alger S, Boyce V, Seagle H, Ferraro R, Fontvieille AM et al. Food intake measured by an automated food-selection system: relationship to energy expenditure. *Am J Clin Nutr* 1992; 55: 343–349. [PubMed: 1734670]
13. Salbe AD, Tschop MH, DelParigi A, Venti CA, Tataranni PA. Negative relationship between fasting plasma ghrelin concentrations and ad libitum food intake. *J Clin Endocrinol Metab* 2004; 89: 2951–2956. [PubMed: 15181083]
14. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2003; 26(Suppl 1): S5–S20. [PubMed: 12502614]
15. Pannacciulli N, Salbe AD, Ortega E, Venti CA, Bogardus C, Krakoff J. The 24-h carbohydrate oxidation rate in a human respiratory chamber predicts ad libitum food intake. *Am J Clin Nutr* 2007; 86: 625–632. [PubMed: 17823426]
16. Geiselman PJ, Anderson AM, Dowdy ML, West DB, Redmann SM, Smith SR. Reliability and validity of a macronutrient self-selection paradigm and a food preference questionnaire. *Physiol Behav* 1998; 63: 919–928. [PubMed: 9618017]
17. Venti CA, Votruba SB, Franks PW, Krakoff J, Salbe AD. Reproducibility of ad libitum energy intake with the use of a computerized vending machine system. *Am J Clin Nutr* 2009; 91: 343–348. [PubMed: 19923376]
18. Herbert V, Lau KS, Gottlieb CW, Bleicher SJ. Coated charcoal immunoassay of insulin. *J Clin Endocrinol Metab* 1965; 25: 1375–1384. [PubMed: 5320561]
19. Brief DJ, Davis JD. Reduction of food intake and body weight by chronic intraventricular insulin infusion. *Brain Res Bull* 1984; 12: 571–575. [PubMed: 6380652]
20. Novin D, Gonzalez MF, Sanderson JD. Paradoxical increased feeding following glucose infusions in recovered lateral rats. *Am J Physiol* 1976; 230: 1084–1089. [PubMed: 817610]
21. VanderWeele DA. Insulin is a prandial satiety hormone. *Physiol Behav* 1994; 56: 619–622. [PubMed: 7972417]
22. VanderWeele DA, Haraczkiwicz E, Van Itallie TB. Elevated insulin and satiety in obese and normal-weight rats. *Appetite* 1982; 3: 99–109. [PubMed: 6753742]
23. Holt SH, Brand Miller JC, Petocz P. Interrelationships among postprandial satiety, glucose and insulin responses and changes in subsequent food intake. *Eur J Clin Nutr* 1996; 50: 788–797. [PubMed: 8968699]
24. Woods SC, Porte D, Jr. Relationship between plasma and cerebrospinal fluid insulin levels of dogs. *Am J Physiol* 1977; 233: E331–E334. [PubMed: 910946]
25. Kaiyala KJ, Prigeon RL, Kahn SE, Woods SC, Schwartz MW. Obesity induced by a high-fat diet is associated with reduced brain insulin transport in dogs. *Diabetes* 2000; 49: 1525–1533. [PubMed: 10969837]
26. Baura GD, Foster DM, Kaiyala K, Porte D, Jr, Kahn SE, Schwartz MW. Insulin transport from plasma into the central nervous system is inhibited by dexamethasone in dogs. *Diabetes* 1996; 45: 86–90. [PubMed: 8522065]
27. Tataranni PA, Larson DE, Snitker S, Young JB, Flatt JP, Ravussin E. Effects of glucocorticoids on energy metabolism and food intake in humans. *Am J Physiol* 1996; 271: E317–E325. [PubMed: 8770026]
28. Schwartz MW, Sipols A, Kahn SE, Lattemann DF, Taborsky GJ, Jr, Bergman RN et al. Kinetics and specificity of insulin uptake from plasma into cerebrospinal fluid. *Am J Physiol* 1990; 259: E378–E383. [PubMed: 2205107]

29. Shrestha YB, Wickwire K, Giraudo SQ. Direct effects of nutrients, acetylcholine, CCK, and insulin on ghrelin release from the isolated stomachs of rats. *Peptides* 2009; 30: 1187–1191. [PubMed: 19463754]
30. Riedy CA, Chavez M, Figlewicz DP, Woods SC. Central insulin enhances sensitivity to cholecystokinin. *Physiol Behav* 1995; 58: 755–760. [PubMed: 8559787]
31. Edgerton DS, Ramnanan CJ, Grueter CA, Johnson KM, Lautz M, Neal DW et al. Effects of insulin on the metabolic control of hepatic gluconeogenesis in vivo. *Diabetes* 2009; 58: 2766–2775. [PubMed: 19755527]
32. Flatt JP. Glycogen levels and obesity. *Int J Obes Relat Metab Disord* 1996; 20(Suppl 2): S1–11.

Figure 1.

Total energy and carbohydrate intake were negatively correlated with iAUC during OGTT. (a–c) Correlation of iAUC with mean of DEI, %WMEN and mean of daily carbohydrate intake. Log10 iAUC, log10 transformed iAUC.

Figure 2.

Correlations of iAUC during OGTT with absolute weight change and percent weight change. (a) absolute weight change; (b) percent weight change. Log10 iAUC, log10 transformed iAUC.

Table 1

Subject anthropometric and caloric intake and weight change variables

	<i>Food intake group</i>	<i>Weight change group</i>
<i>N</i> (M/F)	45/22	214/125
Age (years)	31.3 (7.6)	26.7 (6.8)
BMI (kg m ⁻²)	33.2 (8.9)	31.5 (7.0)
%BF	31.6 (8.3)	30.6 (8.3)
Male	27.2 (6.5)	27.0 (7.4)
Female	38.4 (6.3)	37.5 (6.3)
Fasting insulin (μU ml ⁻¹)	33.1 (28.1–40.3)	33.0 (24.6–42.7)
120-min insulin (μU ml ⁻¹)	120.1 (70.8–149.1)	116 (62.2–179.0)
iAUC (mU ml ⁻¹ per 180 min)	18740.9 (12 023.3–26 409.6)	18450.1 (12 024.2–26 190.4)
Fasting glucose (mmol l ⁻¹)	4.89 (0.37)	4.77 (0.43)
120-min glucose (mmol l ⁻¹)	6.06 (1.11)	5.89 (1.09)
Daily energy intake (kcal per 24 h)	4463.4 (1157.2)	–
Daily carbohydrate intake (g per 24 h)	564.7 (140.7)	–
Daily fat intake (g per 24 h)	192.0 (60.6)	–
Daily protein intake (g per 24 h)	143.3 (41.7)	–
Initial weight (kg)	9 4.7 (27.1)	89.4 (22.0)
Final weight (kg)	–	97.3 (25.2)
Absolute weight change (kg)	–	7.6 (13.3)
Percent weight change (%)	–	0.09 (0.15)
Follow-up time (years)	–	8.5 (6.0)

Abbreviations: BMI, body mass index; iAUC, incremental insulin area under the curve during oral glucose tolerance test; %BF, percentage of body fat.

Data are shown for food intake and weight change two groups. Data are mean (s.d.) or median (25–75% percentile). Absolute weight change calculated as final weight–initial weight; percent weight change calculated as ((final weight–initial weight)/(initial weight × 100%)). Women have higher %BF than men in both food intake and weight change group. %BF was not different between food intake and weight change group.

Sex adjusted Pearson correlation of energy, total carbohydrate, fat and protein intake with age, BMI, %BF and body weight

Table 2

	Age r, P	BMI r, P	% BF r, P	WT r, P
Daily energy intake (kcal per 24 h)	-0.07, 0.57	-0.003, 0.98	-0.07, 0.6	0.05, 0.7
Daily carbohydrate intake (g per 24 h)	-0.11, 0.38	-0.21, 0.1	-0.27, 0.03 ^a	0.16, 0.21
Daily fat intake (g per 24 h)	-0.07, 0.55	-0.08, 0.55	-0.10, 0.45	0.18, 0.15
Daily protein intake (g per 24 h)	-0.19, 0.12	-0.20, 0.12	-0.04, 0.72	0.16, 0.21

Abbreviations: BMI, body mass index; WT, body weight; %BF, percentage of body fat.

^a $P<0.05$.

Table 3

Determinants of weight change

	<i>Weight change (dependent variable)</i>			
	<i>Absolute (kg)</i>		<i>Percent (%)</i>	
	β $r^2 = 0.12$	P P<0.0001	β $r^2 = 0.18$	P P<0.0001
Intercept	24.6	0.0001	0.41	0.0001
Age	-0.38	0.001	-0.005	0.0001
Sex	-0.40	0.58	-0.002	0.72
Initial body weight (kg)	0.03	0.33	-0.0007	0.06
Follow-up time (years)	0.55	<0.0001	0.007	<0.0001
Log10 iAUC	-6.9	0.02	-0.08	0.008

Data are β (estimated partial regression coefficient) and P -values for the association of incremental insulin area under the curve (iAUC) with body weight change as described by absolute and percent weight change after adjustment for covariates. Total R^2 and P -values for the entire model are given. Log10iAUC, log10 transformed iAUC.