Effect of intravenous glucose and euglycemic insulin infusions on short-term appetite and food intake

IAN M. CHAPMAN,1 ELIZABETH A. GOBLE,1 GARY A. WITTERT,1 JOHN E. MORLEY,2 AND MICHAEL HOROWITZ2

1Department of Medicine, Royal Adelaide Hospital, Adelaide, South Australia, Australia 5000; and
2Department of Geriatrics, St. Louis University and Geriatric Research Education and Clinical Center, St. Louis Veterans Affairs Medical Center, St. Louis, Missouri 63104

Chapman, Ian M., Elizabeth A. Goble, Gary A. Wittert, John E. Morley, and Michael Horowitz. Effect of intravenous glucose and euglycemic insulin infusions on short-term appetite and food intake. Am. J. Physiol. 274 (Regulatory Integrative Comp. Physiol. 43): R596–R603, 1998.—To investigate the short-term effects of insulin on feeding, 14 fasting, young adults received 150-min euglycemic intravenous infusions of control (C), low-dose (LD, 0.8 mU·kg⁻¹·min⁻¹), and high-dose (HD, 1.6 mU·kg⁻¹·min⁻¹) insulin and ate freely from a buffet meal during the last 30 min. Steady-state preprandial plasma insulin concentrations were 5.9 ± 0.7 (C), 47 ± 2 (LD), and 95 ± 6 (HD) µU/ml and increased 56–59 µU/ml during the meal. No effect of treatment type on hunger or fullness ratings, duration of eating, or the weight, energy content (1,053 ± 5 kcal, C; 1,086 ± 6 kcal, Glc; P = 0.2), and plasma insulin increased to 45 ± 2.3 µU/ml at the start and 242 ± 36 µU/ml at the end of the meal. Energy intake during the meal was (~15%) reduced (1,072 ± 97 kcal, C; 1,086 ± 102 kcal, LD; 1,088 ± 105 kcal, HD; Glc; P < 0.05 Glc vs. C, LD, and HD). Plasma insulin normally increases to ~100 µU/ml after a mixed meal in lean subjects. Therefore, in the absence of altered blood glucose concentrations, physiological concentrations of insulin are unlikely to play a role in meal termination and the short-term control of appetite.

glucoprivation; feeding; hunger

The role of insulin in the regulation of feeding in humans is controversial. Although exogenous insulin has been reported to increase food intake in both animals and humans (3, 15, 26, 32), these observations may be attributable to glucoprivation and/or a reduction in blood glucose concentrations (relative or absolute hypoglycemia), rather than the effects of insulin itself. In particular, 2-deoxy-o-glucose, which inhibits glucose utilization and induces intracellular glucopenia without affecting plasma insulin concentrations, also increases food intake in humans (35). There is considerable evidence, derived to our knowledge entirely from animal studies, that insulin may inhibit food intake. Central and peripheral administration of insulin reduces food intake in both rodents (4) and baboons (39, 40), provided hypoglycemia is prevented. The physiological significance of these observations is uncertain, as the majority of these studies have involved either the direct injection of insulin into the brain or peripheral administration in pharmacological doses for prolonged periods of time. The observation in rats that central administration of insulin antibodies is associated with an increase in food intake (33) is more persuasive evidence in support of a central appetite-suppressive effect of insulin in that species.

We are not aware of any studies that demonstrate a suppressive effect of insulin on feeding in humans. Rodin et al. (29) performed intravenous hyperinsulinemic hypo- and hyperglycemic clamp studies, the latter using a glucose infusion to stimulate endogenous insulin release, and found that both treatments stimulated short-term appetite and food intake in healthy young adults. They interpreted their results to indicate that insulin stimulates human feeding. Holt and Miller (18) manipulated plasma insulin concentrations physiologically, and higher levels were associated with lessened satiety. Woo et al. (38), on the other hand, found that appetite and food intake in healthy young adults were not affected by intravenous nonhypoglycemic insulin infusions.

Insulin secretion is stimulated more by enteral than intravenous glucose administration due to the incretin effect (22, 25). Enteral glucose administration, whether by the oral or small intestinal route, also suppresses appetite and subsequent food intake more than intravenous glucose administration (28), even when the resultant increase in blood glucose concentration is similar (22). This enhanced appetite suppression could potentially be mediated by the release of incretins, such as glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide, or by other gastrointestinal hormones (8, 12, 20, 36). However, in view of the animal evidence implicating insulin as a satiety agent, it could also be due to the greater insulin release associated with enteral glucose administration. The present study was performed to investigate the short-term effects of insulin on human feeding behavior at concentrations comparable to those seen after a meal.

Methods

Subjects

Fourteen healthy nonsmoking young adult subjects (12 men and 2 woman), 20–33 yr old, with body mass indexes of 20.8–26.7 kg/m² (23.6 ± 1.9, mean ± SD) were studied. All subjects had a score of 10 or less (mean, 4.9 ± 2.6) on the eating restraint factor of the Eating Inventory Questionnaire (34), indicating that they were not restrained eaters, and none was dieting. Both female subjects were taking a combined oral contraceptive pill; otherwise, subjects were not
taking any medications. The protocol was approved by the Human Ethics Committee of the Royal Adelaide Hospital, and subjects gave written informed consent.

Protocol

Study 1. Subjects were studied on the following three occasions, at least 10 days apart: 1) control, 2) 0.8 mU·kg\(^{-1}\)·min\(^{-1}\) insulin (low dose), and 3) 1.6 mU·kg\(^{-1}\)·min\(^{-1}\) insulin (high dose). Studies were performed in random order and single-blind fashion. For females, each study was performed between days 1 and 7 of the oral contraceptive pill treatment cycle. Subjects were advised not to modify their diet throughout the study period and to avoid alcohol and strenuous exercise for at least 24 h before each study. Subjects fasted overnight (nothing except water after 2100 h) and attended the research center the next morning at 0800 h. A cannula was inserted into an arm vein to administer infusions. A second cannula was inserted into a vein of the opposite arm for collection of blood samples; this arm was kept warm using a heating pad to "arterialize" the blood.

The experimental protocol is summarized in Fig. 1. After placement of the cannulas, subjects rested quietly for 30 min. They were then (0 min) asked to record their feelings of hunger and fullness on visual analogue scales (VAS). VAS were administered every 20 min thereafter until 140 min, when a meal was given. Further VAS were administered at the end of the meal (170 min) and at the end of the study (200 min). Venous blood samples were obtained at the same time points for subsequent measurement of plasma insulin and at additional time points for measurement of blood glucose (see below). The intravenous infusion regimens were as follows. From 15 to 170 min, 0.9% saline containing 25 mmol potassium chloride/l was infused intravenously at 200 ml/h. For 2.5 h, from 20 to 170 min, insulin in Haemaccel (Behringwerke, Marburg, Germany) or Haemaccel alone (control) was infused intravenously. The infusion rate was 0.9 ml·kg\(^{-1}\)·h\(^{-1}\) for the first 5 min, 0.7 ml·kg\(^{-1}\)·h\(^{-1}\) for the next 5 min, and then 0.5 ml·kg\(^{-1}\)·h\(^{-1}\) until 170 min. On the low- and high-dose insulin infusion days, regular insulin (Novo-Nordisk Pharmaceutical, North Rocks, New South Wales, Australia) was added to the Haemaccel to produce steady-state insulin infusion rates (30-170 min) of 0.8 and 1.6 mU·kg\(^{-1}\)·min\(^{-1}\), respectively. Twenty-five percent glucose was infused intravenously from 25 to 170 min. The glucose infusion rate was varied according to the results of bedside blood glucose measurements to maintain glucose levels between baseline and baseline plus 10%. The baseline glucose concentration was defined as the mean of the 10- and 15-min values. Bedside testing of blood glucose was performed every 5 to 10 min from 10 to 140 min, at 170 min, and at 200 min, using a portable blood glucose meter (MediSense Companion 2 Blood Glucose System; Medisense, Waltham, MA).

At 140 min, subjects were presented with a cold buffet meal prepared in excess of what they would normally be expected to eat and were instructed to eat as much as they wished (22). The composition of the meal was explained to the subjects at enrollment, and substitute items were arranged when requested. Each subject received the same meal on all three study days. For 11 subjects, the meal consisted of sliced bread (white and whole meal), nondairy spread, mayonnaise, sliced ham, chicken, cheese, tomato and cucumber, lettuce, milk, orange juice, strawberry yogurt, chocolate custard, vanilla ice cream, an apple, pear, and banana. For the other three subjects the meal was the same except that hard-boiled eggs were offered instead of sliced ham and chicken. Subjects were allowed 30 min to eat, during which time the glucose infusion rate was kept constant at the 140-min value. The rate and duration of ingestion and the total amount of food eaten were recorded. At the end of the 30-min meal period, a further venous blood sample was taken, a VAS was administered, and the intravenous glucose, saline, and treatment infusions were stopped.

Study 2. On completion of study 1, the 14 subjects were asked if they would return for a fourth study day. Twelve agreed and returned on the next suitable day. The subjects were not told what treatment they would receive but that the protocol would be similar to one of the previous three visits. The study protocol for this "glucose-only" study day was exactly the same as that of the high-dose insulin study day except that no insulin was administered; for each subject, the glucose infusion exactly reproduced that of their previous high-dose insulin study day.

Assessment of appetite and food intake. Appetite was assessed using 10-cm VAS (31) on which hunger and fullness were quantified. Subjects were familiarized with these scales at the beginning of the study and were instructed to make a single vertical mark on the scale to indicate their current feelings. The 0- and 20-min values were averaged to produce a baseline value, and the changes in ratings from baseline were quantified (22).

Food intake was calculated by weighing each food item before and after the meal. The DIET/1 Nutrient Calculation software package (Yxris Software; Highgate Hill, Queensland, Australia) was used to determine the energy intake (kcal) and macronutrient composition (%protein, %carbohydrate, and %fat) of the meal.

Assays. Plasma insulin was measured using the Abbott IMX Microparticle Enzyme Immunoassay (Abbott Laboratories, Diagnostic Division, Dainabot, Tokyo, Japan). The sensitivity of the assay (concentration at 2 SD from the zero standard) was 1.0 µU/ml. Samples with a value above that of the highest standard (300 µU/ml) were reassayed at a dilution of 1:2. The intra-assay coefficients of the assay were 4% at 8.3 µU/ml, 2.9% at 40.4 µU/ml, and 2.5% at 121.7 µU/ml. The interassay coefficients of variation were 3.7% at 8 µU/ml, 2.8% at 40 µU/ml, and 3.7% at 120 µU/ml.

Statistical analysis. Separate analyses were performed on studies 1 and 2. Twelve of the fourteen subjects took part in both studies and three of their four study days were analyzed as part of both. Differences in appetite ratings at baseline and parameters of food intake were assessed using repeated-measures one-way analysis of variance (ANOVA). Appetite ratings, blood glucose, and plasma insulin concentrations during the studies were assessed using repeated-measures two-way ANOVA, with treatment and time as the factors. Multiple-comparison tests were performed using the Student-Newman-Keuls Test. All calculations were performed using
the SigmaStat program (Jandel Scientific Software, San Rafael, CA). Results are reported as means ± SE. A P value of < 0.05 was considered significant in all analyses.

RESULTS

The study protocol was well tolerated in all subjects, and there were no adverse events.

Study 1

The steady-state glucose infusion rates (mean of 110- to 170-min values) were 0.7 ± 0.1, 7 ± 0.7, and 9 ± 0.7 mg·kg⁻¹·min⁻¹ on the control, low-dose, and high-dose insulin infusion days, respectively. Before the meal, blood glucose concentrations did not differ significantly between the three treatments; all mean concentrations were between 4.8 ± 0.2 and 5.4 ± 0.2 mmol/l (Fig. 2, top). At the end of the meal period (170 min), glucose concentrations were slightly lower on both insulin infusion days than on the control day (control 6.4 ± 0.3, low dose 5.8 ± 0.25, high dose 5.6 ± 0.3 mmol/l, P < 0.02 control vs. high dose and control vs. low dose, P > 0.05 high dose vs. low dose).

On the control day, plasma insulin concentrations were <10 µU/ml until the start of the meal and then increased with food ingestion to 65 ± 9 at the end of the meal period and 81 ± 8 µU/ml 30 min later (Fig. 2, bottom). Plasma insulin concentrations increased within 20 min of the commencement of the low- and high-dose insulin infusions to premeal steady-state levels of 47 ± 2 and 95 ± 6 µU/ml, respectively (mean of 40- to 140-min values). The increases in plasma insulin concentrations during the meal period (140 to 170 min) were not significantly different between the three studies (59 ± 9 control, 56 ± 12 low dose, 57 ± 9 µU/ml high dose, P > 0.05).

Baseline (pretreatment) ratings of hunger (F = 1.8, P = 0.2) and fullness (F = 0.84, P = 0.45) did not differ significantly between the three treatment days. Changes in hunger ratings during the three treatment infusions (baseline to 170 min) are shown in Fig. 3, top. There was an effect of time on hunger (F = 47.2, P < 0.0001); subjects rated themselves as more hungry immediately before the meal and less hungry after the meal than at baseline. There was no effect of treatment type on hunger rating (F = 0.5, P = 0.6) and no interaction between treatment type and time (F = 0.8, P = 0.7). When the analysis was restricted to the time period between baseline and the start of the meal (140 min), there was also a significant effect of time (F = 4.4, P = 0.008), but not treatment type (F = 0.26, P = 0.77), and no interaction between time and treatment type (F = 0.72, P = 0.73).

Changes in ratings of fullness during the treatment infusions are shown in Fig. 3, bottom. There was an effect of time (F = 95, P < 0.0001), with subjects rating themselves as being less full immediately before and more full after the meal than at baseline. There was no effect of treatment type on fullness rating (F = 1.7, P = 0.2) and no interaction between treatment type and time (F = 1.1, P = 0.33). When only the period from baseline to the start of the meal was analyzed, similar effects were observed (time, F = 4, P = 0.001; treat-
ment, \( F = 1.8, P = 0.18 \); time \( \times \) treatment, \( F = 1.2, P = 0.3 \).

No subject ate all of the food offered, and none ate for the full 30 min allotted. The time taken to eat the meal and the weight, energy content, and macronutrient composition of food eaten did not differ significantly between any of the three treatments (Table 1). There was \( <2\% \) difference between the highest and lowest mean energy intakes in response to these three treatments.

**Study 2**

On the glucose-only and high-dose insulin treatment days, \( 328 \pm 25 \) kcal of glucose were infused. Blood glucose concentrations increased during glucose-only infusion to \( 11.7 \pm 0.7 \) mmol/l at 100 min and declined thereafter but, at the start of the meal, remained approximately two times as high as on the other 3 days (Fig. 4, top). The mean glucose concentrations during the four treatment infusions were \( 5.3 \pm 0.1, 5.2 \pm 0.2, 5.2 \pm 0.2, \) and \( 9.3 \pm 0.5 \) mmol/l (\( P < 0.001 \), glucose only vs. the other 3 days).

Plasma insulin concentrations increased progressively during the glucose-only infusion to \( 47 \pm 6 \) \( \mu \)U/ml at the beginning of the meal (Fig. 4, bottom), essentially identical to those at the same time on the low-dose insulin infusion day (\( 45 \pm 2.3 \) \( \mu \)U/ml, \( P > 0.05 \)), and to \( 242 \pm 36 \) \( \mu \)U/ml at the end of the meal. The meal-induced increase in plasma insulin was more than three times greater on the glucose-only infusion day than the three other study days (196 vs. 59, 63 vs. 54, \( 63 \pm 13 \), and \( 54 \pm 10 \) \( \mu \)U/ml, \( P < 0.0001 \), glucose-only day vs. all 3 other days).

Baseline (pretreatment) ratings of hunger (\( P = 0.65 \)) and fullness (\( P = 0.87 \)) did not differ significantly between the four study days. Changes in hunger and fullness ratings during the four treatment infusions (baseline to 170 min) are shown in Fig. 5. There was an effect of time on hunger (\( F = 54.6, P < 0.0001 \)), with subjects rating themselves as being more hungry immediately before the meal and less hungry after the meal than at baseline. There was no effect of treatment type on hunger rating (\( F = 0.4, P = 0.75 \)) and no interaction between treatment type and time (\( F = 0.6, P = 0.9 \)). When the analysis was restricted to the time period between baseline and the start of the meal, there was also a significant effect of time (\( F = 4.3, P = 0.001 \)), but not of treatment type (\( F = 0.34, P = 0.87 \)), and no interaction between time and treatment type (\( F = 0.6, P = 0.9 \)).

**Table 1. Details of test meal consumption in 14 young adult subjects during control conditions and euglycemic iv infusion of insulin**

<table>
<thead>
<tr>
<th>Food Intake</th>
<th>Insulin, ( \text{mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</th>
<th>Control</th>
<th>0.8</th>
<th>1.6</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration, min</td>
<td>21.2 ( \pm ) 1.5</td>
<td>19.7 ( \pm ) 1.6</td>
<td>19.5 ( \pm ) 1.6</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Weight, g</td>
<td>999 ( \pm ) 97</td>
<td>981 ( \pm ) 96</td>
<td>1,001 ( \pm ) 99</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Energy, kcal</td>
<td>1,053 ( \pm ) 95</td>
<td>1,045 ( \pm ) 101</td>
<td>1,066 ( \pm ) 107</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Carbohydrate, %</td>
<td>47 ( \pm ) 1.1</td>
<td>49 ( \pm ) 1.5</td>
<td>46 ( \pm ) 0.9</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Fat, %</td>
<td>33 ( \pm ) 1</td>
<td>31 ( \pm ) 1.3</td>
<td>33 ( \pm ) 1</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Protein, %</td>
<td>20 ( \pm ) 0.7</td>
<td>20 ( \pm ) 0.6</td>
<td>20 ( \pm ) 0.6</td>
<td>0.7</td>
<td></td>
</tr>
</tbody>
</table>

Values are means \( \pm \) SE. \( P \) values for comparison between groups by repeated-measures analysis of variance (ANOVA).

**Fig. 4.** Mean \( \pm \) SE venous glucose concentrations (top) and plasma insulin concentrations (bottom) during iv infusion of 25% glucose (\( \circ \)) and euglycemic iv infusions of control (\( \bullet \)), low-dose insulin (\( \square \)), and high-dose insulin (\( \triangle \)); \( n = 12 \).

**Fig. 5.** Change from baseline in ratings of hunger (top) and fullness (bottom) during iv infusion of 25% glucose (\( \circ \)) and euglycemic iv infusions of control (\( \bullet \)), low-dose insulin (\( \square \)), and high-dose insulin (\( \triangle \)); \( n = 12 \). Significant effect of time on hunger and fullness (\( P < 0.01 \) by ANOVA) but no significant effect of treatment on either hunger or fullness.
When the total infusion period (baseline to 170 min) was analyzed, there was an effect of time on fullness (F = 125, P < 0.0001), with subjects rating themselves as less full immediately before the meal and more full after the meal than at baseline. There was no effect of treatment type on fullness (F = 0.35, P = 0.8) and no interaction between treatment type and time (F = 0.7, P = 0.8). The same was so when only the period between baseline and the start of the meal was analyzed (time, F = 2.9, P = 0.014; treatment, F = 0.3, P = 0.8; time × treatment, F = 0.8, P = 0.7). Notwithstanding the absence of a significant effect (as assessed by ANOVA) of treatment type on ratings of hunger and fullness, there was a trend toward greater fullness and less hunger at 140 min (immediately before the start of the meal) on the glucose-only infusion day than on any of the other three treatment days (Fig. 5).

The durations of eating, weight, energy content, and macronutrient composition of food eaten are shown in Table 2. There was an effect of treatment type on energy intake (F = 4.1, P = 0.015), which was significantly (−15%) lower on the glucose infusion day than any of the other treatment days, none of which was different from each other. There was no effect of study order on energy intake in the first three study days, when the treatments were randomized (1,096 ± 101, 1,090 ± 106, and 1,060 ± 97 kcal, F = 0.27, P = 0.8).

**Table 2.** Details of test meal consumption in 12 healthy young adult subjects during control conditions, iv infusion of glucose, or euglycemic iv infusion of insulin

<table>
<thead>
<tr>
<th>Food Intake</th>
<th>Control</th>
<th>Insulin, mU·kg⁻¹·min⁻¹</th>
<th>Glucose</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration, min</td>
<td>21.2 ± 1.5</td>
<td>20.1 ± 1.6</td>
<td>19.6 ± 1.3</td>
<td>19.1 ± 1.7</td>
</tr>
<tr>
<td>Weight, g</td>
<td>997 ± 103</td>
<td>1,017 ± 97</td>
<td>1,026 ± 96</td>
<td>894 ± 112</td>
</tr>
<tr>
<td>Energy, kcal</td>
<td>1,072 ± 97</td>
<td>1,086 ± 102</td>
<td>1,088 ± 105</td>
<td>919 ± 115</td>
</tr>
<tr>
<td>Carbohydrate, %</td>
<td>47 ± 1.3</td>
<td>49 ± 1.7</td>
<td>46 ± 1</td>
<td>49 ± 2.1</td>
</tr>
<tr>
<td>Fat, %</td>
<td>33 ± 1.1</td>
<td>32 ± 1.4</td>
<td>34 ± 1.1</td>
<td>31.5 ± 1.8</td>
</tr>
<tr>
<td>Protein, %</td>
<td>20 ± 0.7</td>
<td>19 ± 0.6</td>
<td>20 ± 0.7</td>
<td>19.5 ± 0.8</td>
</tr>
</tbody>
</table>

Values are means ± SE. Glucose infusion was same 25% glucose infusion as on insulin (1.6 mU·kg⁻¹·min⁻¹) treatment day but no insulin was infused. P values for comparison between groups by repeated-measures one-way ANOVA. *P < 0.05, 25% glucose day vs. control and 0.8 and 1.6 mU·kg⁻¹·min⁻¹ insulin by Student-Newman-Keuls test.

The change in energy intake from that on the control day [energy intake (treatment day) − energy intake (control day; kcal)] and the change in premeal fullness (P = 0.47) or hunger (P = 0.55) ratings from those on the control day, when all three interventions (low-dose insulin, high-dose insulin, and glucose only) were analyzed together. However, when the glucose-only day alone was compared with the control day, there was a significant positive correlation between the change in energy intake and hunger ratings (r = 0.67, P = 0.02) and a negative correlation between changes in energy intake and fullness ratings, which did not quite achieve significance (r = 0.56, P = 0.057).

**DISCUSSION**

The results of this study indicate that, under euglycemic conditions, intravenous insulin administration has no short-term effects on appetite ratings or food intake in young adults of normal body weight. In fasting, lean, subjects, plasma insulin concentrations increase to a mean peak of ~100 µU/ml, ~30-60 min after the start of a mixed meal and then return to baseline within 2-4 h (14). In the present study, insulin infusions were started 2 h before the test meal and were continued throughout the meal; mean steady-state preprandial plasma insulin concentrations on the low- and high-dose insulin infusion days were 47 and 95 µU/ml, respectively, compared with a mean peak insulin concentration of 81 µU/ml after a moderately large meal on the control day. Thus the infusion-induced increases in plasma insulin concentrations quite closely reproduced, in both duration and magnitude, the normal postprandial rise. In contrast to the lack of effect on feeding of euglycemic insulin infusions, infusion of glucose only significantly suppressed food intake and was associated with a nonsignificant suppression in appetite ratings. In the study as a whole, preprandial hunger ratings correlated positively, and fullness ratings correlated negatively, with food intake at the subsequent meal. The lack of any stimulatory effect of insulin on appetite ratings and food intake in this study, in which hypoglycemia (and hence glucoprivation) was avoided, provides indirect evidence that the increase in appetite and food intake that accompanies insulin-induced hypoglycemia (13, 29) is due to glucoprivation.

Our findings are consistent with those of Woo et al. (38), who administered intravenous insulin and glucose infusions to young, nonobese, adult subjects, starting 30 min before and finishing 15 min after a test meal, for a total duration of ~55 min. In a separate part of the same study, subjects ate a small amount of food 12 min before the test meal to induce endogenous insulin release and then received an insulin-glucose infusion for ~21 min from the beginning of the meal. Neither insulin infusion affected appetite or food intake compared with control infusions. In that study, preprandial plasma insulin concentrations were ~35-40 µU/ml, lower than often observed after a mixed meal, and blood glucose concentrations were not matched on the control and treatment days in the first part of the study.
Short-term effects of insulin on feeding, particularly at higher physiological postprandial plasma concentrations, therefore could not be totally excluded. We have extended the findings of Woo et al. by demonstrating that longer-duration (2.5 h) euglycemic insulin infusions, which produce plasma insulin concentrations as high as those after a normal meal, also have no short-term effect on appetite in humans. Intravenous insulin infusions produce sustained increases in cerebrospinal fluid insulin concentrations within 30–45 min of their commencement (37), so it is likely that the brain, a proposed site of insulin effects on feeding (30), was exposed to elevated insulin levels for most of the insulin infusion period in this study.

It should be recognized that our study design did not allow examination of several possible effects of insulin on feeding behavior. First, the timing of food ingestion was fixed, so that the subjects had no control over when they ate. Insulin could potentially affect the timing of spontaneous food ingestion. In a series of elegant studies using animals and humans, free to eat when they wished, Campfield et al. (5, 6) showed that the timing of spontaneous food ingestion is related to transient decreases in blood glucose concentration within the nonhypoglycemic range, implying that a reduction in glucose levels may trigger food intake. It is conceivable that such decreases are related to increases in insulin secretion or action, but this is probably unlikely given that they occur in the fasting state, some time after a meal. We are not aware of studies that have addressed this issue.

Our study was designed specifically to evaluate the effects of insulin and not to reproduce in every detail a normal physiological state. The infusions were performed after an overnight fast, and it may be inappropriate to extrapolate the findings to times later in the day when meals are spaced more closely. Nevertheless, the duration of the overnight fast is not so great that appetite ratings and food intake cannot be affected by further changes within the physiological range. This is indicated by the increasing ratings of hunger and decreasing ratings of fullness during the two preprandial hours of the euglycemic infusions in this study, as well as our previous observations, using a similar study design, that appetite ratings and food intake in fasting young adults are significantly suppressed by intraduodenal infusions of relatively modest amounts (340 kcal over 2 h) of glucose (22) or lipid (9).

In healthy, lean individuals, an increase in plasma insulin levels normally occurs in the postprandial rather than the fasting state. Food ingestion stimulates the secretion of a number of gastrointestinal hormones, besides insulin, which may affect feeding. They include glucagon (12), amylin (8), cholecystokinin (12, 20), and GLP-I (16, 36). Animal studies suggest that the interaction of insulin with these hormones may have synergistic effects on appetite. For example, in nonhuman primates, central administration of low-dose insulin can enhance the satiating effects of peripherally administered cholecystokinin (11). It is theoretically possible that, because secretion of these gastrointestinal hor-
the portal (and peripheral) circulations, provides no evidence for such an effect.

In the second part of the study, glucose was infused intravenously without insulin to match the amount and timing of the glucose infusion on the high-dose insulin day. During the glucose-only infusion, ratings of hunger were decreased and ratings of fullness were increased compared with the other three infusion days. Although these differences were not statistically significant, they are consistent with the suppressive effect of this infusion on food intake. Energy intake during the test meal was ~15% less than during the control and insulin infusions, despite the peak preprandial plasma insulin concentration being essentially the same as on the low-dose day and one-half that on the high-dose insulin day. The absolute meal-induced increase in plasma insulin concentrations was much greater on the glucose-only infusion day than the other 3 days, even though less food was eaten, due to the priming effect of prior glucose exposure on pancreatic insulin release (7). In animals, short-term intravenous glucose infusions apparently have little, if any, suppressive effect on food intake (see Ref. 28 for review), and prolonged infusions are required to produce marked suppression. In baboons, for example, there is a significant reduction in food intake during the 14- to 21-day intravenous glucose infusions, but this suppressive effect takes several days to develop and is not maximal until about day 10 (40). The effect of intravenous glucose on human appetite is less clear and has even been reported to increase appetite and food intake (29). There are a number of possible explanations for the reduced food intake observed with glucose infusion in this study.

By necessity, the treatment order of this study could not be randomized, and an order effect cannot be excluded. All subjects received the glucose-only infusion on their fourth and final study day to match the infusion rate exactly to that on the high-dose insulin day. The subjects may therefore have eaten less because they were being presented with the same meal for the fourth time and were tired of it. However, the lack of a significant order effect on food intake during the first three randomized euglycemic studies perhaps makes this explanation unlikely. The trend toward increased fullness ratings and decreased hunger ratings preprandially on the glucose-only day may suggest that subjects were experiencing reduced appetite even before being presented with the meal. It is possible that the effects of endogenous and exogenous insulin on food intake differ. Such a difference has not been demonstrated but could occur as a result of the secretion of endogenous insulin into the portal circulation and passage through the liver before entering the peripheral circulation. Alternately, exogenous and endogenous insulin may exert the same qualitative effects on feeding, and the suppression in this study reflects a dose-responsive effect of portal insulin concentrations on food intake, as discussed.

The hyperglycemia induced by glucose-only infusion could potentially have mediated the associated suppression of food intake; blood glucose concentrations during this infusion were almost double those during the other three treatment infusions (9.3 vs. 5.2–5.3 mmol/l). It has been difficult to examine the effect of elevated blood glucose concentrations on feeding, largely because of the problems involved in manipulating blood glucose levels while insulin levels and the amount of nutrient administered are kept constant. Over 40 years ago, Mayer proposed that food intake is modulated by variations in blood glucose concentrations (24), but increased emphasis has since been placed on the rate of glucose utilization and the availability of glucose for cellular oxidative processes (28). Although hepatic glucose production is suppressed during both intravenous glucose infusions and euglycemic hyperinsulinemic clamp studies, there is evidence that hyperglycemia exerts a suppressive effect independent of and additional to that of hyperinsulinemia (10). Intravenous infusion of glucose enhances splanchnic glucose uptake, whereas euglycemic infusion of insulin resulting in plasma insulin levels up to 20 times higher does not. The hyperglycemia-induced enhancement of splanchnic glucose uptake may be dependent on coexistent hyperinsulinemia (10). Hyperglycemia is also associated with slowing of gastric emptying (23) and increased perception of fullness in both diabetic (19) and nondiabetic subjects (17), potential mechanisms by which it could exert suppressive effects on feeding. Therefore, although most studies suggest that any suppressive effect of hyperglycemia per se is likely to be minor (22, 28, 40), one could speculate that the independent effects of hyperglycemia on glucose utilization and/or its effects on gastrointestinal motility and perceptions could be responsible for the different effects on appetite observed in the two parts of our study. Or, as discussed, hyperinsulinemia and hyperglycemia may interact to inhibit appetite and food intake, whereas each factor alone is without effect.

Last, it is possible that a factor (or factors) cosecreted with endogenous insulin in response to intravenous glucose is responsible for the suppression of food intake by intravenous glucose in this study. Many hormones with possible satiating effects are secreted in response to intravenous glucose, albeit in smaller amounts than after oral glucose ingestion. They include GLP-1 and amylin; both have been shown to reduce food intake in animal studies (8, 36), and GLP-1 has recently been reported to reduce appetite and food intake in humans (16).

In summary, we have established that 2.5-h euglycemic insulin infusions, producing plasma insulin concentrations equivalent to those normally achieved after a meal, have no effect on ratings of hunger and fullness or voluntary food intake in young adults. This finding suggests that, by itself, insulin does not affect short-term feeding behavior and is consistent with a previous report that physiological hyperinsulinemia is without effect on short-term food intake (38). Long-term effects of insulin on food intake, if proven to exist in humans, are likely to be secondary to metabolic effects of insulin and not insulin per se. The observation that intravenous glucose infusion results in a modest reduction in
food intake may indicate the effect of hyperglycemia, of another glucose-induced “postprandial” factor, or an interaction between hyperinsulinemia and such a factor.

I. M. Chapman was supported by a Pharmacia Research Fellowship of the Royal Australasian College of Physicians.

Address for reprint requests: I. Chapman, Dept. of Medicine, Royal Adelaide Hospital, North Terrace, Adelaide, South Australia, Australia 5000.

Received 5 June 1997; accepted in final form 29 October 1997.

REFERENCES


