Thermic Effect of Infused Glucose and Insulin in Man

DECREASED RESPONSE WITH INCREASED INSULIN RESISTANCE IN OBESITY AND NONINSULIN-DEPENDENT DIABETES MELLITUS

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ABSTRACT The thermic effect of infused glucose and insulin was measured by combining the hyperinsulinemic euglycemic clamp technique with indirect calorimetry, in 10 normal weight volunteers (group I), 7 obese subjects with normal glucose tolerance (group II), and 13 obese subjects with abnormal glucose tolerance or noninsulin-dependent diabetes mellitus before (group IIIa) and after weight loss of 10.8±0.4 kg (group IIIb).

During hyperinsulinemia (760-1,100 pmol/liter), total glucose disposal from combined endogenous production and glucose infusion was 545±49, 441±70, 233±35, 231±31 mg/min and energy expenditure changed by +0.476±0.080, +0.293±0.095, -0.114 ±0.063, and +0.135±0.082 kJ/min in group I, II, IIIa, and IIIb, respectively. The increased energy expenditure correlated with glucose storage (measured cost of processing the glucose: 1.33 kJ/g). In group IIIa there was no increase in energy expenditure in response to glucose and insulin infusions. After therapy (group IIIb) there was a significant recovery ($P < 0.05$) of the thermic effect of infused glucose although total glucose disposal was unchanged. It is proposed that the recovered thermic effect of infused insulin/glucose is due to the different contributions of gluconeogenesis in the fasting state and during the glucose clamp before and after weight loss. In addition we hypothesize that some of the lower thermic effect of food reported in obese noninsulin-dependent diabetics may be explained by decreased energy expenditure due to a greater suppression of hepatic gluconeogenesis as well as by lower storage rate.

INTRODUCTION

An increase in metabolic rate associated with ingestion of food has been well documented (1-5). Recently, a reduced thermic effect of a meal in obese subjects, in comparison with that of normal weight subjects, has been reported, (6-10). It has been postulated that this decreased dietary-induced thermogenesis might be involved in the etiology of obesity or the maintenance of the obese state. However, the mechanism by which it occurs is not known.

By combining the hyperinsulinemic euglycemic clamp technique with measurements of respiratory exchange (11) it has been possible to study the thermic effect of glucose infusion in more detail than before. Recently it has been estimated that ~50–70% of the increment in energy expenditure associated with a glucose infusion in normal weight subjects can be accounted for by the cost of glucose storage alone (12, 13).

It has been demonstrated using the insulin/glucose clamp technique that obese and noninsulin-dependent diabetic subjects are insulin resistant and that glucose uptake under these conditions is reduced (14).

In the present study we have used these two techniques to investigate and compare the thermic effect of insulin/glucose infusions in three groups of subjects with different degrees of insulin resistance: 10 healthy normal weight individuals, 7 obese glucose-tolerant subjects, and 12 obese glucose-intolerant and/or noninsulin-dependent diabetic patients.[1] The obese glu-

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[1] The 12 obese glucose-intolerant and/or noninsulin-dependent diabetes mellitus patients were involved in a more extensive study.

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cose-intolerant subjects were further studied after a weight reducing regimen that included dietary therapy with or without added physical training.

The goal of the study was to investigate a possible relationship between glucose-induced thermogenesis and insulin resistance.

METHODS

Subjects

29 subjects were divided into three groups (Table I) according to their medical history and glucose tolerance.

Group I. 10 subjects (6 males and 4 females) of normal weight (71.0±5.7 kg; 16.3±1.6% fat) who had maintained their body weight for several months before the study and had no family history of diabetes mellitus or obesity.

Group II. Seven obese subjects (three males and four females) (98.2±8.2 kg; 33.6±1.8% fat) with normal glucose tolerance in response to oral ingestion of 75 g of glucose (Glucola). They all had >25% body fat. Their fasting and 2-h postingestion plasma glucose concentrations were <5.5 mM and 7.8 mM, respectively.

Group IIIa. 12 obese subjects (97.5±6.1 kg; 37.3±2.3% fat) (1 male and 11 females) of whom 11 had >25% body fat, 7 were diabetic according to the National Diabetes Group criteria (15), and all were glucose intolerant with fasting glucose values >5.5 mM (range: 5.7 to 11.6) and 2-h postabsorptive glucose >7.8 mM.

Group IIIb. The same subjects (group IIIa) were studied further after a weight reducing program.[1] They all followed a hypocaloric, high-fiber diet calculated to provide 1,885 kJ (450 kcal)/m² of their initial body surface area [average daily intake 3,850 kJ (920 kcal)] per day with a composition of 25% protein, 15% fat, and 60% carbohydrate and 25–30 g of dietary fiber. This diet was followed for 12 wk, after which the meal plans were adjusted to maintain the new weight (10.8±0.4 kg lower than the initial weight) for a further 10–14 d before the study was repeated. Six of them were also involved in a physical training program. No significant differences were observed in weight loss, composition of weight loss, fasting plasma glucose, and insulin concentrations between the six subjects involved in physical training and those who dieted without added exercise.[1]

Experimental protocol

The experimental protocol, which was reviewed by the University of Vermont Committee on Human Experimentation, was presented in detail to the subjects, who gave their informed consent before participating in the study. They were then given a full medical history and physical examination, which also included the measurement of body composition by underwater weighing (16) with correction for residual lung volume by helium dilution. From the measured body density, the fraction of body fat was calculated using Siri's equation (17).

Euglycemic insulin clamp with measurement of endogenous glucose production

After an 11-h overnight fast, an indwelling catheter was placed in an antecubital vein for infusion of 20% glucose,

porcine insulin (Iletin, II, Eli Lilly & Co., Indianapolis, IN), and dideuterated glucose (99%, [6,6,d₂]glucose, KOR Isotopes, Cambridge, MA; Merck, Sharp, and Dohme, Toronto, Canada). Arterialized blood samples (18) were obtained from an indwelling catheter inserted into a dorsal hand vein of the other arm. The hand was kept in a preheated warming box at 68°–70°C for the duration of the test (3 h for group I, 5 h for group II, and 5–7 h for group IIIa and IIIb). 0.5 h after the insertion of the catheters, a primed-continuous infusion of tracer amounts of dideuterated glucose was begun in groups II, IIIa, and IIIb to estimate the hepatic glucose production in the basal state (2 h) and during the glucose and insulin infusion. Hepatic glucose production was not determined in the 10 healthy normal weight subjects (group I), as nearly complete suppression of hepatic glucose production has been reported in normal subjects (19–21).

The hyperinsulinemic euglycemic clamp was performed as described by DeFronzo et al. (22). A primed continuous (40 mU/m²·min) infusion of insulin was administered acutely to raise and maintain the serum insulin concentration approximately between 760 and 1,100 pM/liter (106–153 μU/ml). Blood was drawn every 5 min for plasma glucose determination, every 10 min for serum insulin determination and for [6,6-d₂]glucose enrichment, and every 30 min for measurements of plasma epinephrine and norepinephrine concentrations (in groups I and II). Plasma glucose was maintained constant at ~5.0 mM by varying a 20% glucose infusion. In group IIIa, depending on the fasting plasma glucose concentration, the start of the glucose infusion varied from 10 to 120 min after the initiation of the insulin infusion.

On a separate day, 6 of the 10 normal weight subjects (group I) and the 7 obese subjects of group II underwent a control study, which was identical to that of the euglycemic clamp experiments except that insulin and glucose infusions were replaced by infusion of 0.9% saline. The order of the control and experimental tests were randomized for these 13 subjects.

Respiratory exchange measurements

The energy expenditure and the rate of substrate utilization were measured by indirect calorimetry for 1 h before (four air collections of 5 min) and every 15 min throughout the clamp procedure as previously described (12). During each collection, the subject breathed through a low resistance "J" valve (Warren E. Collins, Braintree, MA). After 2 min of adaptation the expired air was collected in a 120-liter Tissot spirometer (Warren E. Collins). A sample of expired air was continuously drawn, physically dried by means of an ice-cooled trap, and analyzed for oxygen by a zirconium fuel cell O₂ analyzer (Applied Electrochemistry, Sunnyvale, CA) and for carbon dioxide by an infrared CO₂ analyzer (Gould and Godart, De Bilt, Holland). The analyzers were calibrated before and after the procedure using room air and a 5.00% CO₂ and 15.00% O₂ standard gas. The total volume of expired air corrected for STP conditions, and the O₂ and CO₂ concentration each second, were read as an electrical output by a Hewlett-Packard 85 computer (Hewlet-Packard Co., Palo Alto, CA) through an analog-digital converter interface. Corrections were applied for the eventual reading drifts of the analyzers. The nonprotein respiratory quotient (NPRQ) was then calculated from the respiratory exchange data and the urinary urea nitrogen production rates. The oxidation rates of carbohydrate and lipid were calculated according to the tables of Lusk (23), which are based on a 0.707 nonprotein respiratory quotient for 100% fat oxidation

and 1.000 for 100% carbohydrate oxidation rates. The quantity of urinary urea nitrogen excreted during the study period was used as an index of protein oxidation, assuming that the latter is constant (1 g N = 6.25 g protein).

Analytical procedures

Plasma glucose concentrations were determined by the glucose oxidase method using a glucose analyzer (model 23A, Yellow Springs Instrument Co., Yellow Springs, OH). Serum immunoreactive insulin concentrations were determined by a modification of the radioimmunoassay technique of Starr et al. (24). Plasma epinephrine and norepinephrine concentrations were determined for groups I and II using a radioenzymatic assay kit (Upjohn Co., Kalamazoo, MI). Urinary urea nitrogen was measured by a Technicon autoanalyzer (Technicon Instruments Corp., Tarrytown, NY). Glucose enrichment was determined by means of a gas chromatographic mass spectrometer (model 5985B, Hewlett-Packard Co.) on the pentacetate derivative of glucose, using electron impact ionization and selectively monitoring ions at m/e 200.1 and 202.1. During the basal period, the steady-state equations of Steele (25) were used to calculate the rate of glucose appearance, and during the variable glucose infusion, the nonsteady-state equations of Steele (25), assuming a glucose distribution volume of 40 ml/kg body wt (26).

Data calculation and analysis

The last 30 min of the glucose-insulin clamp study and the last 30 min of the base-line period (before the start of the insulin infusion) were used for comparison between the four groups. The rate of glucose uptake by the entire body (M) was considered to be the sum of the rates of glucose infusion and endogenous glucose production. The nonoxidative glucose disposal, which includes storage, was calculated as the difference between the rate of carbohydrate oxidation and the total uptake of glucose by the entire body.

The change in energy expenditure (kilojoule per minute) during each clamp study was estimated as the difference in the mean energy expenditure during the last 30 min of the base-line period and the energy expenditure during the last 30 min of the insulin/glucose infusion. The theoretical cost of storing the glucose as glycogen was based on the estimate that 2 mol ATP (5.3%), out of the 38 mol theoretically available from a total oxidation of the glucose, are required to store 1 mol of glucose as glycogen (27). The cost of this process was calculated by multiplying the energy content of the glucose stored (15.65 kJ/g) by 5.3% (2/38).

Results are presented as mean±SEM. Statistical comparisons were performed by paired t test (intragroup or group IIIa and IIIb) or unpaired t test (intergroup). Simple and multiple linear regression analyses were used for comparison of variables.

RESULTS

Mean fasting plasma glucose and serum insulin concentrations are presented in Table I. The subjects of group IIIa had fasting plasma glucose concentrations ranging from 5.7 to 11.6 mM, and six had values > 6.5 mM. After therapy (group IIIb), individual fasting glucose concentrations decreased by 0.3–1.3, averaging 0.7 mM. The serum insulin concentrations during the insulin infusions rose to 760±28, 928±76, 1,102±81, and 1,023±65 pmol/liter in groups I, II, IIIa, and IIIb, respectively (group I vs. groups IIIa and IIIb, P < 0.05). These differences are probably related to differences in insulin sensitivity between group I and groups IIIa and IIIb and to differences in the clearance rate of the insulin. The increased insulin concentration during the studies of the obese and diabetic subjects would be expected to give a greater thermogenic response, contrary to what was found. During the clamp study, the plasma glucose concentrations were maintained at 5.0 mM in all subjects with a coefficient of variation of 2.8±0.2, 4.0±0.4, 2.2±0.1, and 2.2±0.1% in group I, II, IIIa, and IIIb, respectively.

TABLE I

Physical Characteristics, Fasting Plasma Glucose and Fasting Serum Insulin Concentrations, Basal Endogenous (Hepatic) Glucose Production, and Base-line Resting Metabolic Rate of 10 Normal Weight Subjects (Group I), 7 Obese with Normal Glucose Tolerance (Group II), and 12 Obese with Abnormal Glucose Tolerance or Noninsulin-dependent Diabetes Mellitus Before (Group IIIa) and After (Group IIIb) Weight Loss (12 wk)

	Age	Weight	Body fat	FFM	Fasting plasma glucose	Fasting serum insulin	Hepatic glucose production	Resting metabolic rate
	yr	kg	%	kg	mmol/liter	pmol/liter*	mg/min	KJ/24 h × kg FFM
Group I	38±3	71.0±5.7	16.3±1.6	59.7±5.1	5.2±0.1	29±3	—	104±2
Group II	31±2	98.2±8.2‡	33.6±1.8‡	65.6±6.4	5.3±0.1	77±18‡	191±17	111±3
Group IIIa	42±3	97.5±6.1‡	37.3±2.3‡	60.0±2.4	7.1±0.5‡§	160±27‡§	225±23	116±3‡
Group IIIb	42±3	86.7±5.1‡‖	33.3±2.5‡	56.8±2.2‖	6.4±0.4‡‖	105±20‡‖	166±13‖	109±3‖

Data represent mean±SEM.
* 7.175 pmol/liter = 1μU/ml.
‡ Statistically different from group I (P < 0.05).
§ Statistically different from group II (P < 0.05).
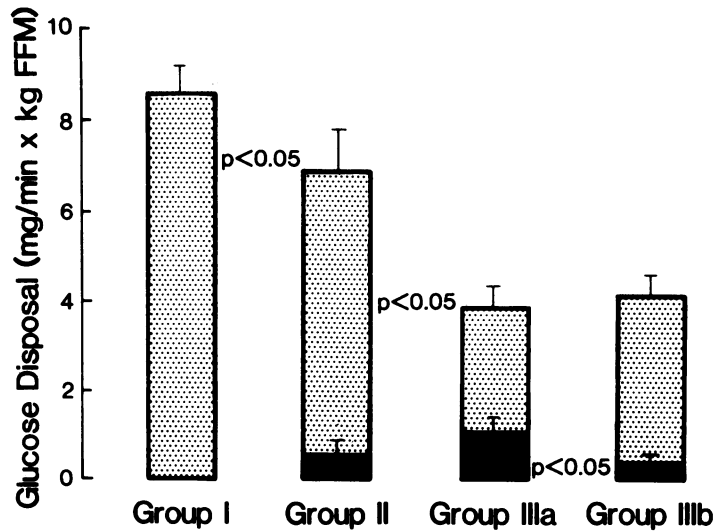‖ Statistically different from group IIIa (P < 0.05).

FIGURE 1 Total glucose disposal rate during a euglycemic-hyperinsulinemic clamp procedure (90–120 min) in 10 normal-weight, healthy volunteers (group I), 7 obese with normal glucose tolerance (group II), and 12 obese with abnormal glucose tolerance before (group IIIa) and after (group IIIb) loss of 10.8±4 kg of body weight through physical training and/or diet therapy. The results are expressed per kilogram of FFM. The solid areas represent the endogenous glucose production, whereas the hatched areas represent the exogenously infused glucose. The total glucose disposal rate was significantly lower ($P < 0.05$) in group IIIa in comparison with that of group II and lower ($P < 0.05$) in group II in comparison with that of group I, indicating a progressive decrease in peripheral insulin sensitivity in groups I–IIIa. The residual endogenous glucose production was greater in group IIIa (before treatment) than in group IIIb (after treatment) ($P < 0.05$); there was therefore no significant difference in total glucose disposal between the two groups. Data represent mean + SEM.

Euglycemic hyperinsulinemic glucose clamp with measurement of endogenous glucose production. The basal endogenous glucose production was 191±17 mg/min in group II, 225±23 mg/min in group IIIa, and 166±13 mg/min in group IIIb (IIIa vs. IIIb; $P < 0.05$) (Table I). During the last 30 min of the glucose clamp procedure, the endogenous glucose production rates were decreased to 31±14, 66±24, and 25±9 mg/ min, representing an 84, 71, and 85% suppression of the basal endogenous glucose production rate in groups II, IIIa, and IIIb, respectively. The relative percent suppression during the glucose/insulin infusion was greater in group IIIb than in group IIIa ($P < 0.001$), whereas the absolute suppression in milligrams per minute was greater in group IIIa when compared with group IIIb ($P < 0.05$).

The total glucose disposal (M) rates (infusion plus endogenous production) were 545±49, 441±70, 233±35, and 231±31 mg/min in group I, II, IIIa, and IIIb, respectively. In the normal weight subjects who

were not resistant to insulin (group I), the "M" value correlated better with fat-free mass (FFM)[2] than with the total body weight. Expressed on this basis, the glucose disposal was 8.6±0.5, 6.9±0.9, 3.8±0.5, and 4.1±0.5 mg/min kg FFM in group I, II, IIIa, and IIIb, respectively (Fig. 1). In group IIIb, when compared to group IIIa, the higher glucose infusion rate ($P < 0.01$) was compensated for by a lower endogenous residual glucose production rate ($P < 0.05$) resulting in no change in total glucose disposal rate.

Respiratory exchange measurement. The fate of the infused glucose is presented in Fig. 2. The postabsorptive respiratory quotients (RQ) were 0.795±0.011, 0.819±0.013, 0.763±0.017, and 0.767 ±0.013 in groups I, II, IIIa, and IIIb, respectively. The RQ rose significantly during the clamp procedure reaching values of 0.903±0.015, 0.904±0.013, 0.820±0.014, and 0.845±0.013 during the last 30 min of the test, indicating increased carbohydrate oxidation stimulated by the insulin/glucose infusion. The basal and stimulated RQ were significantly lower ($P < 0.01$) in groups IIIa and IIIb in comparison with those of groups I and II, indicating lower carbohydrate oxidation rates in these subjects. However, when groups IIIa and IIIb were compared, only carbohy-

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[2] Abbreviations used in this paper: FFM, fat-free mass; RQ, respiratory quotient(s); SNS, sympathetic nervous system.
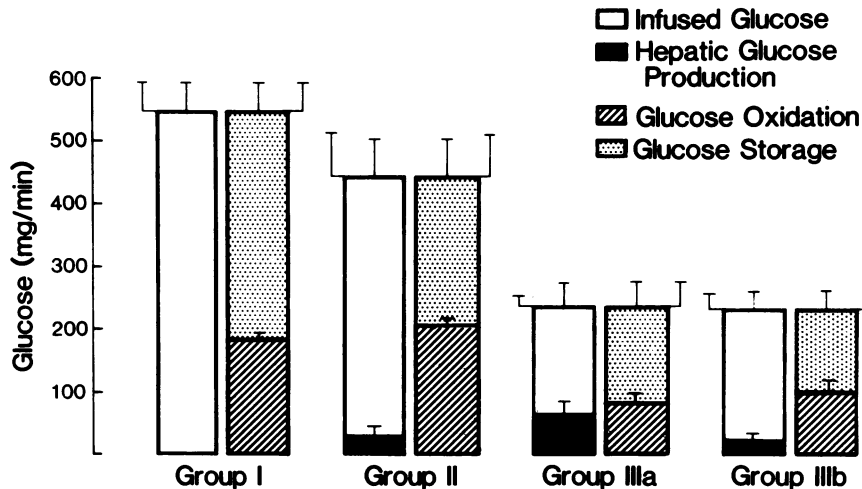
FIGURE 2 Total glucose disposal rate (90–120 min) (*left* column) of exogenous (infused) and endogenous (mainly hepatic) origin. Subjects as in Fig. 1. The glucose disposal rate (*left* column) is equal to the glucose uptake rate (*right* column), which can be divided (by the indirect calorimetric method) into glucose oxidized and glucose nonoxidatively disposed (including storage). The glucose storage rate was significantly reduced ($P < 0.05$) from group I to II and from group II to IIIa and IIIb. The bars are means + SEM.

drate oxidation was improved by weight reduction, (86 ± 14 to 104 ± 13 mg/min; $P < 0.01$), whereas no change in nonoxidative disposal was observed. When expressed per kilogram FFM, nonoxidative disposal rates of carbohydrate were significantly decreased from group I to II ($P < 0.05$) and from group II to IIIa ($P < 0.05$). The base-line resting metabolic rates were 4.295 ± 0.360, 4.959 ± 0.346, 4.780 ± 0.167, and 4.247 ± 0.122 kJ/min in groups I, II, IIIa, and IIIb, respectively. During the last 30 min of the glucose clamp, the increase in energy expenditure above base-line values averaged 0.476 ± 0.080 kJ/min in group I ($P < 0.05$) and 0.293 ± 0.095 kJ/min in group II ($P < 0.05$), representing an increase of 11.1 and 5.9% in energy expenditure during the insulin/glucose infusion, respectively (Fig. 3). In both groups, the progressive increase in energy expenditure over time was correlated with the progressive increase in glucose infusion. There was no statistical change in energy expenditure during the insulin/glucose infusion in group IIIa and IIIb. However, the tendency for the energy expenditure to decrease in the subjects of group IIIa (-0.114 ± 0.063 kJ/min) during the insulin infusion was reversed after weight loss ($+0.135\pm0.082$ kJ/min) ($P < 0.05$). 10 of the 12 subjects showed a greater response after weight loss. In the five subjects of group IIIa in whom the glucose infusion was started at least 35 min after beginning the insulin infusion, there was a decline ($P < 0.05$) in energy expenditure from 5.156 ± 0.254 kJ/min during the base-line period to 4.970 ± 0.215 kJ/min during the insulin infusion. The

changes in energy expenditure during the euglycemic clamp before and after weight loss were correlated by multiple regression analysis, both with the changes in total glucose nonoxidative disposal ($P < 0.05$) and the changes in endogenous glucose production ($P < 0.05$), with a total coefficient of correlation of 0.613 ($P < 0.05$). This indicates that both glucose nonoxidative disposal and suppression of endogenous glucose production during the clamp procedure contribute to the changes in energy expenditure during a hyperinsulinemic euglycemic clamp procedure. There was no change in resting metabolic rate during the control study (normal saline infusion) either in the six subjects from group I, or in the seven obese subjects from group II.

The thermogenic response measured during the insulin/glucose infusions, and the predicted response for glucose storage are shown in Fig. 3. Glucose storage could explain 66 ± 5, 62 ± 10, and $78\pm18\%$ of the measured response in groups I, II, and IIIb, respectively. The absolute increase in energy expenditure correlated with the rate of glucose storage (nonoxidative glucose disposal) in group I ($r = 0.855$; $P < 0.001$), II ($r = 0.872$; $P < 0.01$), and IIIb ($r = 0.531$; $P < 0.05$) whereas no correlation was observed in group IIIa ($r = 0.228$; NS). Since there was only a significant correlation between the change in energy expenditure and the net glucose storage rate in groups I, II, and IIIb, and since there was no difference in the slopes of the three regression lines, the data of these three groups were combined in a single correlation presented
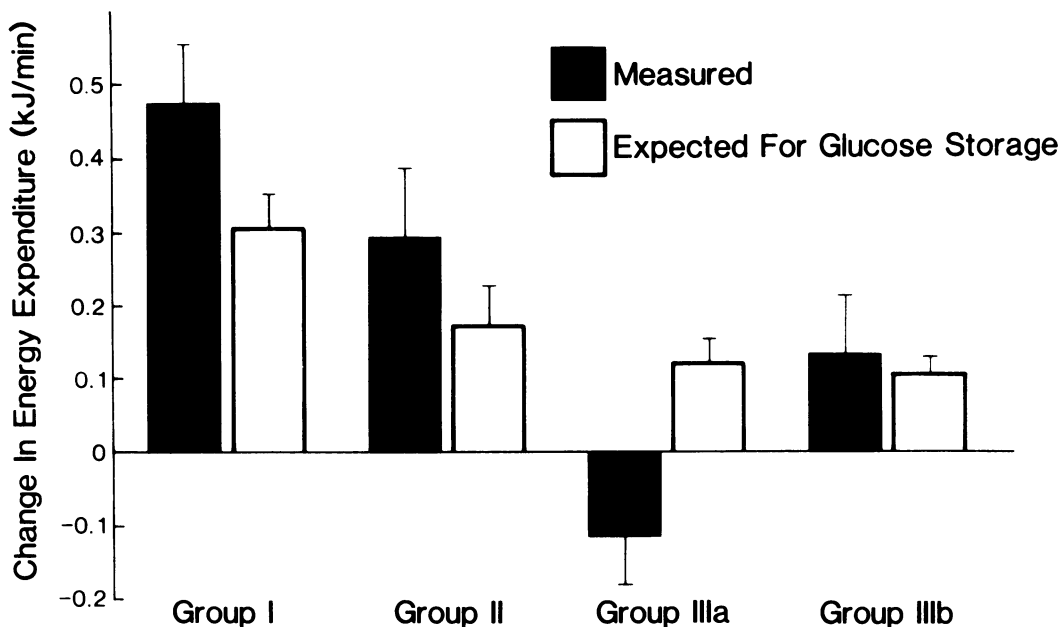
FIGURE 3 Changes in energy expenditure (solid bars) measured during a euglycemic hyper-insulinemic clamp procedure. Subjects as in Fig. 1. The tendency toward a decrease in energy expenditure in group IIIa was significantly ($P < 0.05$) reversed after weight loss (group IIIb). The white bars in each group represent the expected cost of glucose storage, assuming that 5.3% of the glucose energy content (1 g = 15.65 kJ) is required for its conversion to glycogen (see Discussion). Means + SEM are presented.
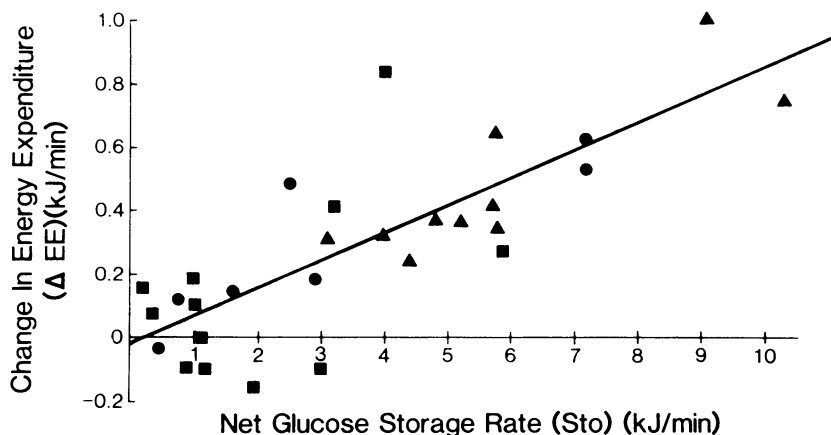

FIGURE 4 Correlation between the change in energy expenditure (EE) (90–120 min) during insulin and glucose infusion compared with base line, and the glucose storage rate (glucose storage = glucose disposal − carbohydrate oxidation). 1 g of glucose is assumed to be equivalent to 15.65 kJ. The 10 normal weight, healthy volunteers are represented by triangles (▲), the 7 obese with normal glucose tolerance by circles (●), and the 12 obese after weight loss by squares (■). The 12 obese with impaired tolerance before weight loss (group IIIa) are not included in this correlation, since in this group changes in energy expenditure and glucose apparent storage were not correlated. The slope of the regression line indicates that 8.5% of the stored calories are dissipated as heat. This is an effect of the storage process (∼60%) and other factors such as increased SNS activity, glucose recycling, and protein turnover (see Discussion). ΔEE = −0.016 + 0.085 storage; r = 0.787.

in Fig. 4 (r = 0.787; P < 0.001). The slope of the regression line indicates that ~8.5% of the energy content of the glucose stored by the body was dissipated as heat, at a measured cost of 1.33 kJ/g of glucose stored. This correlation was still significant when the results of group IIIa were included (r = 0.672; P < 0.001), with a slope of 0.083.

Plasma catecholamines. In the control subjects (group I), the base-line plasma norepinephrine concentrations varied from 104 to 420 pg/ml, the highest value being observed in the oldest subject. The plasma norepinephrine concentrations increased significantly from 204±30 pg/ml during the base line (mean of two samples) to 227±39 pg/ml (P < 0.05) during the euglycemic clamp (average of 90 and 105 min sample), i.e., an increase of 10±3%. There was no change during the control study. In the seven obese subjects (group II) there was a slight increase in the mean plasma norepinephrine concentration during the glucose clamp (129±11 vs. 148±11 pg/ml) and the control study (131±7 vs. 143±12 pg/ml), however, these changes were not statistically significant. There was no change in concentrations of plasma epinephrine during the euglycemic clamp or the control study in groups I or II. Plasma catecholamines were not measured in group IIIa and IIIb.

DISCUSSION

The thermic effect of infused insulin/glucose was studied in three groups of subjects with differing degrees of insulin resistance. An inverse relationship was found between the thermic effect of infused insulin/glucose and insulin resistance. In fact, in our most insulin resistant group (group IIIa), no apparent thermic effect was observed.

After a mean weight reduction of 10.8 kg (group IIIb), however, the thermic effect of infused insulin/glucose was partially restored when compared with that in the same subjects before therapy, or with the control or obese nonglucose intolerant groups. Since the restoration of the thermic effect of infused insulin/glucose correlated both with the changes in glucose storage and suppression of endogenous glucose production, it can be postulated that the thermic effect of glucose is the net result of two major components: (*a*) the increase in energy expenditure due to the energy cost of glucose storage. When glucose is converted into glycogen, ~5.3% of the energy content of glucose is required for this process (27); (*b*) the decrease in energy expenditure due to the suppression of endogenous glucose production, primarily hepatic gluconeogenesis, an energy-requiring process.

In normal weight healthy subjects, the rate of hepatic glucose production is ~0.8–1.0 mmol/min in the postabsorptive resting state (28). Of this, 75–84% is due to glycogenolysis and the remainder to gluconeogenesis from lactate, pyruvate, glycerol, and the glucogenic amino acids, primarily alanine (29, 30). Formation of glucose from lactate, pyruvate, or alanine are all energy-requiring processes. In type I diabetics, total hepatic glucose output is high and the contribution of glucogenic precursors is increased, accounting for 32% of the total hepatic glucose output (31). In obese noninsulin-dependent diabetics (type II) a high splanchnic uptake of glucogenic precursors has also been reported (32). These reports suggest that there is a higher rate of basal gluconeogenesis in these patients than in normal healthy subjects. In view of their glucose intolerance and their decreased peripheral and hepatic insulin sensitivity in the fasting state, the subjects in group IIIa not only had higher rates of apparent hepatic glucose production (160±16 vs. 140±5 mg/min in groups IIIa and IIIb, respectively) but it is likely that they also had higher rates of gluconeogenesis than subjects of groups I, II, and IIIb.

Hepatic glucose production is almost completely suppressed during a 1 mU/kg min insulin clamp in lean healthy subjects given plasma insulin concentrations of 720–900 pM/liter (100–125 μU/ml) (19–21). This suppression is mainly due to the diversion of newly formed glucose into glycogen rather than to decreased gluconeogenesis (33). However, gluconeogenesis is far more sensitive to small increments in insulin when it is proceeding at a high rate as it presumably was in our type II diabetics before weight loss.[3] In the diabetic dog, administration of insulin results in a significant inhibition of gluconeogenesis (34).

In our insulin-resistant group (IIIa) it is very likely that gluconeogenesis was occurring at a high rate. This is indirectly supported by two facts. The resting metabolic rate was higher (P < 0.05) in group IIIa than in groups I and IIIb both when expressed in absolute as well as in relative terms (kilojoule per kilogram FFM) (Table I). This is in contrast to our previous finding that the resting metabolic rate does not differ between lean subjects and nondiabetic obese when related to FFM (35). Secondly, a statistically significant decrease in metabolic rate was observed when only insulin was infused to reduce glycemia to 5 mM in these subjects early during the clamp procedure, suggesting suppression of gluconeogenesis.

Thus, when glucose was infused to maintain glycemia at 5 mM, the thermic effect of the low rate (and cost, ~5%) of glycogen storage was exceeded by the relatively greater suppression (and cost, ~10%) of gluconeogenesis. Furthermore, other mechanisms such as

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[3] Cherrington, A. D. Personal communication.

activation of the sympathetic nervous system, increased protein turnover, and increased Na-K-ATPase activity, might be blunted in insulin-resistant subjects, and this might also contribute to the decreased thermic effect of infused insulin/glucose.

After weight reduction the increased thermic response to insulin/glucose infusion in the absence of an improved glucose storage rate could be explained by a lower basal rate of hepatic glucose production and gluconeogenesis (note significant decrease in fasting metabolic rate, Table I), therefore, a smaller absolute suppression of gluconeogenesis during the clamp procedure. The possible restoration of other mechanisms may also contribute to the improved thermic effect of infused insulin/glucose in the obese type II diabetic after weight loss.

It was found that the change in metabolic rate in these studies correlated well with the rate of glucose storage ($r = 0.787$, $P < 0.001$, Fig. 4). However, no correlations were observed between the changes in metabolic rate and plasma insulin or plasma norepinephrine (groups I and II). The slope of the regression (8.5%) represents the proportion of glucose energy required to store the infused glucose as glycogen. This is greater than the theoretical value for this process, 5.3% (27). Although glucose storage as glycogen represents the major component of the increase in the nonoxidative energy expenditure (62% on average [12]) other factors discussed below must also contribute to the thermic effect of insulin/glucose infusion.

Mechanisms that might explain this additional increase in metabolic rate during conditions of hyperinsulinemic euglycemia are: (a) increased sympathetic nervous system (SNS) activity (36); (b) de novo lipogenesis (37); (c) recycling of glucose as three-carbon compounds (Cori cycle or glucose-alanine cycle); (d) other futile cycles of metabolism; and (e) stimulation of other energy requiring processes including protein turnover and Na-K-ATPase activity.

Of these different processes, which have been more fully discussed elsewhere (12, 13), it is unlikely that de novo lipogenesis contributed to the thermogenic response. Although it is an energy-requiring process (~21% of the glucose energy) (27), most of the glucose infused during an insulin/glucose clamp is taken up by muscle tissue, which lacks several key lipogenic enzymes (37).

Significant increases in plasma norepinephrine concentrations have been observed in normal weight volunteers after oral (5) and infused (12, 36) glucose administration consistent with increased SNS activity (38). Although the quantitative thermogenic effect of physiologically liberated norepinephrine is not known, it is possible that the observed rise in norepinephrine

contributed to part of the unexplained rise (35–40%) in energy expenditure.

This study has demonstrated that the thermic effect of infused insulin/glucose is inversely related to the degree of insulin resistance and that in obese insulin-resistant subjects it can be completely abolished. This observation is important in relation to the observed blunted thermogenic response to a glucose load in obese (6–9) or diabetic obese subjects (10) when compared with nonobese individuals. However, it is still unclear whether obesity per se is the cause of the reported blunted thermogenic response to a meal. Our results support the concept that the decreased thermogenic response to the administration of glucose can be partially restored by weight loss, which suggests that this thermogenic defect is the consequence rather than the cause of obesity. Recently, Schwartz et al. (9) have shown in four obese patients who have lost weight a trend toward normalization in the thermic response to feeding. More studies in which the thermic effect of a meal is measured both before and after weight gain and loss need to be performed to answer the question of the origin of the defect in thermogenic response associated with obesity and insulin resistance. Most of the cited studies in which the thermic effect of a meal was measured have been conducted over periods of only 3–4 h. Since the thermic effect of a mixed or a pure carbohydrate meal lasts longer than this, it is likely that part of the response was not measured in these studies. A decrease in the thermic effect of a carbohydrate meal could also be due to a relatively greater suppression of gluconeogenesis in response to the meal, as suggested by this study. In the current study the thermic effect of glucose has been evaluated at the end of the clamp procedure when a steady state has been reached and when the rate of glucose disposal is known.

The present findings are consistent with those of Cunningham et al. (39) in their studies of efficiency of weight gain in rats fed a varied "cafeteria" diet. Those animals that developed an impairment of tolerance to intravenous glucose had the greater efficiency of weight gain and thus the least increase in adaptive thermogenesis. By combining respiratory exchange measurements and the hyperinsulinemic euglycemic clamp procedure, it has been possible to estimate the separate components of the thermic effect of carbohydrate in man. The thermic effect is mainly related to the cost of nonoxidative glucose disposal, of which a major component is presumably storage, whereas other mechanisms including increased SNS activity may also be involved. With increased insulin resistance, the lower thermic effect of infused insulin/ glucose is a consequence of lower carbohydrate storage

rates (40) and possibly a greater absolute inhibition of gluconeogenesis.

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