Thermic effect of glucose in man. Obligatory and facultative thermogenesis.

K J Acheson, … , J Wahren, E Jéquier

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Research Article

The contribution of the sympathetic nervous system to the thermic effect of intravenously infused glucose and insulin was studied in 10 healthy young men before and after beta-adrenergic receptor blockade with propranolol during conditions of normoglycemia (90 mg/dl) at two levels of hyperinsulinemia (approximately 90 microU/ml and approximately 620 microU/ml). During steady state conditions of glucose uptake (0.515 +/- 0.046 and 0.754 +/- 0.056 g/min), significant increases were observed in energy expenditure (0.10 +/- 0.02 kcal/min, P less than 0.001, and 0.21 +/- 0.02 kcal/min, P less than 0.01, respectively). Similarly, glucose oxidation increased from 0.100 +/- 0.015 to 0.266 +/- 0.022 g/min (P less than 0.001) at approximately microU/ml insulin and from 0.082 +/- 0.013 to 0.295 +/- 0.018 g/min (P less than 0.001) at approximately 620 microU/ml insulin. Concomitantly, the rate of nonoxidative glucose disposal or "glucose storage" was 0.249 +/- 0.033 and 0.459 +/- 0.048 g/min, respectively. At this time the thermic effect of infused glucose/insulin was 5.3 +/- 0.9 and 7.5 +/- 0.7%, and the energy cost of "glucose storage" was 0.50 +/- 0.16 kcal/g and 0.47 +/- 0.04 kcal/g at the two different levels of glucose uptake. After beta-adrenergic receptor blockade with propranolol, glucose uptake, oxidation, and "storage" were unchanged in both studies, but significant decreases in energy expenditure were observed (1.41 +/- 0.06-1.36 +/- […]

Thermic Effect of Glucose in Man

Obligatory and Facultative Thermogenesis

K. J. Acheson, E. Ravussin, J. Wahren, and E. Jéquier
Institute of Physiology, University of Lausanne, Switzerland, and Department of Clinical Physiology, Karolinska Institute, Huddinge Hospital, S-141 86 Stockholm, Sweden

Abstract. The contribution of the sympathetic nervous system to the thermic effect of intravenously infused glucose and insulin was studied in 10 healthy young men before and after β-adrenergic receptor blockade with propranolol during conditions of normoglycemia (90 mg/dl) at two levels of hyperinsulinemia (~90 μU/ml and ~620 μU/ml).

During steady state conditions of glucose uptake (0.515±0.046 and 0.754±0.056 g/min), significant increases were observed in energy expenditure (0.10±0.02 kcal/min, $P < 0.001$, and 0.21±0.02 kcal/min, $P < 0.01$, respectively). Similarly, glucose oxidation increased from 0.100±0.015 to 0.266±0.022 g/min ($P < 0.001$) at ~90 μU/ml insulin and from 0.082±0.013 to 0.295±0.018 g/min ($P < 0.001$) at ~620 μU/ml insulin. Concomitantly, the rate of nonoxidative glucose disposal or "glucose storage" was 0.249±0.033 and 0.459±0.048 g/min, respectively. At this time the thermic effect of infused glucose/insulin was 5.3±0.9 and 7.5±0.7%, and the energy cost of "glucose storage" was 0.50±0.16 kcal/g and 0.47±0.04 kcal/g at the two different levels of glucose uptake.

After β-adrenergic receptor blockade with propranolol, glucose uptake, oxidation, and "storage" were unchanged in both studies, but significant decreases in energy expenditure were observed (1.41±0.06–1.36±0.05 kcal/min, $P < 0.01$ at ~90 μU/ml insulin, and 1.52±0.07–1.43±0.05 kcal/min, $P < 0.005$ at ~620 μU/ml insulin) causing significant falls in both the estimated thermic effect of infused glucose/insulin and the energy cost of "glucose storage".

Regression analysis of the results from both studies indicated a mean energy cost for "glucose storage" of 0.36 kcal/g ($r = 0.74$, $P < 0.001$), which fell significantly ($P < 0.005$) to 0.21 kcal/g ($r = 0.49$, $P < 0.05$) during β-adrenergic receptor blockade with propranolol. The latter is in close agreement with that calculated on theoretical grounds for the metabolic cost of glucose storage as glycogen, i.e., obligatory thermogenesis.

It is concluded that β-adrenergically mediated sympathetic nervous activity is responsible for almost the entire rise in energy expenditure in excess of the obligatory requirements for processing and storing glucose during conditions of normoglycemia and hyperinsulinemia in healthy man, and that the energy cost of "glucose storage" is not different at normal (~90 μU/ml) and supraphysiological (~620 μU/ml) plasma insulin concentrations.

Dr. Acheson is on secondment from the Research Department, Nestlé Products Technical Assistance Co. Ltd., Case postale 88, CH-1814 La Tour-de-Peilz, Switzerland. Address correspondence to Dr. Acheson, Institute of Physiology, 7 Rue du Bugnon, 1011 Lausanne, Switzerland.

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Introduction

Recently, the heat increment, or the thermic effect of food, has been divided into an obligatory component that relates to the digestion, absorption, and processing of nutrients, and into a regulatory or facultative component that is due to energy expended in excess of the obligatory demands (1). In animals, this facultative thermogenesis has been attributed mainly to sympathetic nervous stimulation of brown adipose tissue thermogenesis after a meal (2, 3).

In man, increased plasma norepinephrine levels have been observed both after carbohydrate ingestion (4) and glucose/insulin infusions (5). Morgan et al. (6) have demonstrated decreased thermic responses to food and ephedrine in "energetically efficient" individuals and Jung et al. (7) have observed reduced thermogenesis in obesity during norepinephrine infusions. Thus, the sympathetic nervous system would seem to play a role, which is difficult to quantitate, in the stimulation of energy expenditure after meal ingestion in man.

In a previous study (8) the hyperinsulinemic, hyperglycemic clamp technique was used in combination with indirect calorimetry and propranolol infusion to investigate the influence of β-adrenergic receptor blockade on the thermic effect of combined hyperglycemia and hyperinsulinemia. Under the

conditions of the study, ~30% of the thermic effect of infused glucose and insulin could be attributed to sympathetic nervous stimulation. The conditions of our previous study were chosen to exaggerate the rise in glucose storage and energy expenditure in order to emphasize a possible sympathetic component, and did not allow a differentiation between the effect of hyperinsulinemia alone and that of combined hyperglycemia and hyperinsulinemia. Rowe et al. (5) have demonstrated that plasma norepinephrine concentrations are greater during hyperinsulinemia than hyperglycemia, and Rothwell and Stock (3) have suggested that insulin per se could be thermogenic. Consequently, in the present study we have used two levels of hyperinsulinemia, one physiological (~90 μU/ml) and the other supraphysiological (~620 μU/ml) in combination with normoglycemia to investigate both the influence of insulin and a range of glucose uptakes upon the energy cost of "glucose storage" before and after β-receptor blockade with propranolol.

Methods

Subjects. Ten healthy male subjects with an average age of 25 yr (range 22–32 yr), height 180 cm (range 170–192 cm), and weight 71.3 kg (range 64–76 kg) volunteered for the study. All subjects were informed of the nature, purpose, and possible risks involved in the study before giving their consent to participate. No subject had a medical history of diabetes mellitus or respiratory ailments and none were taking any medication. All were consuming their habitual diet, which was supplemented with sugared fruit juice for 2 d before the test, to ensure that the diet contained at least 250 g carbohydrate. The study protocol had previously been accepted by the institutional ethics committee.

Experimental protocol. All studies were performed after an overnight fast. Each subject spent the night before the study in a room adjoining that in which the test was performed. On the morning of the test, the subject was awoken at 6:30 a.m., and, after voiding, was transferred to the test room where two peripheral venous catheters were inserted, one into an antecubital vein for the infusion of all test substances and the other retrogradely into a wrist vein for blood sampling. The hand was then placed in a heated box (70°C) to achieve arterialization of the venous blood. 1 h before beginning the infusions, continuous respiratory exchange measurements were begun and continued throughout the duration of the experimental protocol. Energy expenditure and substrate utilization were determined by computerized open-circuit, indirect calorimetry using a ventilated hood system (9). Heart rate and blood pressure were monitored every 5 min, using a Dinamap (Applied Medical Research Corp., Tampa, FL) blood pressure recorder, with the inflatable cuff attached to the arm that was not used for infusion and blood sampling.

Nine subjects participated in each study, eight of whom volunteered for both series of experiments and were studied at an interval that ranged from 1 to 8 wk. Each subject served as his own control.

In study 1, after 1 h of base-line measurements, the subject received a primed continuous infusion of insulin (Actrapid; Novo Industri S/A, Bagsvaerd, Denmark) at a rate of 1 mU/kg·min for 4 h. Blood glucose concentration was maintained at 90 mg/dl throughout the study by determination of the plasma glucose concentration every 5 min and periodically adjusting a variable intravenous infusion of 20% glucose solution (10). After 2 h of hyperinsulinemic normoglycemia, a bolus of propranolol was given (50 μg/kg body weight) and then infused at a rate of 1 μg/kg·min for a further 2 h. Arterialized venous blood samples were collected in the basal state and at timed intervals throughout the study for analysis of substrate and hormone concentrations. Urine was collected before and after the study for nitrogen determination.

In study 2, the subjects repeated the same protocol as above with the exception that a primed continuous infusion of insulin at 5 mU/kg·min was maintained throughout the 4-h study period. Propranolol was administered as in study 1. We have previously demonstrated that propranolol at the doses that were employed in the present study has no effect upon postabsorptive resting metabolic rate, and that there is no spontaneous fall in energy expenditure during a 4 h hyperinsulinemic, hyperglycemic clamp without propranolol (8).

Analytical methods. Plasma glucose was determined in duplicate by the glucose oxidase method on a Beckman glucose analyzer (Beckman Instruments Inc., Fullerton, CA). Plasma insulin (11) and C-peptide levels were measured by radioimmunoassay, catecholamines were analyzed using high performance liquid chromatography technique (12, 13); and blood urea nitrogen was analyzed using a Technicon (Technicon Corp., Tarrytown, NY) autoanalyzer (14). Plasma free fatty acid concentrations were determined on a Dole extract (15, 16). Urinary nitrogen was measured by the Kjeldahl method (17).

Data analysis. Whole body glucose uptake during insulin and glucose administration was calculated from the rate of glucose infusion that was required to maintain euglycemia. For data presentation, the mean value for the last 40 min from −40–0, 80–120 and 200–240 min are given. Energy expenditure and substrate utilization were calculated from the oxygen consumption, carbon dioxide production, and urinary nitrogen excretion (18) after correction for changes in the body urea nitrogen pool (19). Since glucose, rather than starch or glycogen, was the major energetic substrate in these studies, glucose oxidation was calculated using the value 0.746 liters oxygen consumed per gram glucose oxidized, instead of 0.829 liters oxygen per gram starch oxidized (18).

The rate of "glucose storage" or nonoxidative glucose disposal was calculated by subtracting the rate of glucose oxidation from the rate of steady state glucose uptake, assuming complete inhibition of endogenous glucose production (20). Using this value, the energy cost of "glucose storage" was estimated by dividing the increase in metabolic rate, above the base-line value, by the rate of glucose storage.

The thermic effect of infused glucose/insulin was calculated by dividing the increase in metabolic rate above basal (kilocalories per minute), during steady state conditions, by the rate of glucose energy uptake (kilocalories per minute) during the same period. This value was compared with a theoretically derived value based on an estimated metabolic cost of converting glucose to glycogen of 5.3% (21). Data in the text, tables, and figures are given as mean±SE. Standard statistical methods have been employed using the paired *t* test when applicable.

Results

The postabsorptive resting metabolic rates before the glucose/insulin infusions were identical (1.31±0.06 kcal/min) in studies 1 and 2 (Tables I and II). In study 1, plasma insulin levels rose from a basal value of 10.9±1.3 to 85±4 μU/ml during the 80–120-min period of the insulin clamp (Table III). Glucose uptake at this time was 0.515±0.046 g/min (7.17±0.46 mg/kg·min; Table I and Fig. 1) and was accompanied by significant increases in metabolic rate from 1.31±0.06 to

Table I. Study 1. Metabolic and Circulatory Variables during the Hyperinsulinemic Clamp Study (1 mU/kg · min)

	Basal (−40–0 min)	P	Hyperinsulinemia ≃90 μU/ml (80–120 min)	P	Hyperinsulinemia ≃90 μU/ml plus propranolol (200–240 min)
Metabolic rate (*kcal/min*)	1.31±0.06	0.001	1.41±0.06	0.01	1.36±0.05
Glucose uptake (*g/min*)			0.515±0.046	NS	0.553±0.033
"Glucose storage" (*g/min*)			0.249±0.033	NS	0.279±0.026
Cost of "glucose storage" (*kcal/g*)			0.50±0.13	0.05	0.17±0.04
Thermic effect of infused glucose/insulin (%)			5.3±0.9	0.005	2.3±0.6
Heart rate (*beats/min*)	60±2	0.02	66±2	0.001	57±2
Systolic blood pressure (*mmHg*)	126±3	NS	126±4	0.02	122±3
Diastolic blood pressure (*mmHg*)	68±2	NS	66±3	NS	63±2

NS, not significant.

1.41±0.06 kcal/min ($P < 0.001$), in glucose oxidation from 0.100±0.015 to 0.266±0.022 g/min ($P < 0.001$), and in heart rate ($P < 0.02$). In addition, a significant decrease in lipid oxidation from 0.067±0.005 to 0.029±0.004 g/min was observed ($P < 0.001$).

After propranolol administration in study 1, energy expenditure decreased by 4% to 1.36±0.05 kcal/min ($P < 0.01$, 200–240 min, Fig. 3), while insulin increased slightly to 94±4 μU/ml ($P < 0.05$). Concomitantly slight, but nonsignificant increases in glucose uptake (0.553±0.033 g/min, 7.54±0.4 mg/kg · min), glucose oxidation (0.274±0.013 g/min), and "glucose storage" (0.279±0.026 g/min) were observed (Fig. 1), with the result that the proportion of the glucose uptake that was oxidized and "stored" remained approximately the same before and during propranolol, i.e., ~50% (Figs. 1 and 3). However, a significant decrease was observed in the energy cost of "glucose storage" (0.50±0.13–0.17±0.04 kcal/g, $P < 0.05$) and the thermic effect of infused glucose/insulin (5.3±0.9–2.3±0.6%, $P < 0.005$). Moreover, both heart rate (66±2–57±2 beats/min, $P < 0.001$) and systolic blood pressure (126±4–122±3 mmHg, $P < 0.02$) decreased significantly after propranolol administration (Table I).

In study 2, the plasma insulin levels rose from a basal level of 10.1±1.0 to 615±29 μU/ml ($P < 0.001$) during the 80–

Table II. Study 2. Metabolic and Circulatory Variables during the Hyperinsulinemic Clamp Study (5 mU/kg · min)

	Basal (−40–0 min)	P	Hyperinsulinemia ≃620 μU/ml (80–120 min)	P	Hyperinsulinemia ≃620 μU/ml plus propranolol (200–240 min)
Metabolic rate (*kcal/min*)	1.31±0.06	0.001	1.52±0.07	0.005	1.43±0.05
Glucose uptake (*g/min*)			0.754±0.056	NS	0.754±0.034
"Glucose storage" (*g/min*)			0.459±0.048	NS	0.459±0.031
Cost of "glucose storage" (*kcal/g*)			0.47±0.04	0.001	0.26±0.04
Thermic effect of infused glucose/insulin (%)			7.5±0.7	0.001	4.2±0.6
Heart rate (*beats/min*)	59±3	0.001	68±3	0.001	58±2
Systolic blood pressure (*mmHg*)	126±3	NS	130±4	0.02	123±4
Diastolic blood pressure (*mmHg*)	68±3	NS	68±3	0.001	62±2

NS, not significant.

Table III. Study 1. Blood Parameters during 1 mU/kg · min Insulin Clamp

	Basal (−40–0 min)	P	Clamp (80–120 min)	P	Clamp plus propranolol (200–240 min)
Insulin (*μU/ml*)	10.9±1.3	0.001	85±4	0.05	94±4
C-peptide (*ng/ml*)	1.51±0.08	0.001	0.84±0.07	NS	0.85±1.0
Free fatty acids (*μmol/l*)	403±19	0.001	165±4	NS	151±8
Blood urea nitrogen (*mmol/l*)	4.7±0.2	0.05	4.3±0.3	0.001	3.8±0.2
Norepinephrine (*nmol/l*)	1.00±0.10	0.05	1.29±0.14	0.02	1.63±0.15
Epinephrine (*nmol/l*)	0.20±0.05	NS	0.26±0.06	0.02	0.45±0.10

NS, not significant.

120-min period (Table IV) and significant increases were observed in metabolic rate (+16%, $P < 0.001$). Moreover, glucose uptake rose to 0.754±0.056 g/min (Fig. 2) and glucose oxidation increased from 0.082±0.013 to 0.295±0.018 g/min ($P < 0.001$). Finally, heart rate rose from 59±3 to 68±3 beats/min ($P < 0.001$), while blood pressure remained unchanged. As in study 1, lipid oxidation fell from 0.082±0.008 to 0.032±0.007 g/min ($P < 0.001$).

By the end of the propranolol infusion in study 2, insulin levels had risen slightly (+2%). However, no significant changes were observed in glucose uptake (Table II), glucose oxidation, or "glucose storage", as compared with before propranolol (Figs. 2 and 3). Metabolic rate fell by 6% to 1.43±0.05 kcal/min ($P < 0.005$, Fig. 3), with corresponding decreases in the calculated energy cost of "glucose storage" (0.47±0.04–0.26±0.04 kcal/g, $P < 0.001$) and the thermic effect of infused glucose/insulin (7.5±0.7–4.2±0.6%, $P < 0.001$). Significant decreases were also observed in heart rate (68±3–58±2 beats/min, $P < 0.001$) and systolic and diastolic blood pressure (Table II). Since eight subjects completed both study 1 and 2, it was possible to compare the results of the two tests directly (Table V).

Due to higher steady state insulin levels in the second experiment, glucose uptake was greater in study 2 (+45%, $P < 0.005$), which resulted in a higher metabolic rate (+9%, $P < 0.005$). Although glucose oxidation was only slightly greater in study 2—reaching statistical significance at the end of the propranolol infusion—"glucose storage" was much greater (+75%, $P < 0.001$) in study 2.

By plotting the individual increase in energy expenditure over basal against the rate of "glucose storage", it is possible to obtain a regression, the slope of which represents the energy cost of "glucose storage" (Fig. 4). During glucose/insulin infusion without propranolol, a relationship was observed in which the energy cost of "glucose storage" was found to be 0.36 kcal/g of glucose stored. β-adrenergic receptor blockade caused a decrease in energy expenditure, which reduced the energy cost of "glucose storage" to 0.21 kcal/g. When the two

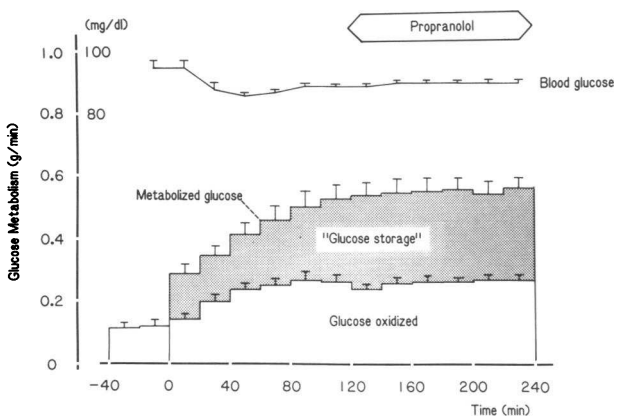

Figure 1. Blood glucose (mg/dl) and the contribution of glucose oxidation and "glucose storage" to the rate of metabolized glucose (g/min) at plasma insulin levels of ~90 μU/ml. The period 80–120 min (without propranolol) was compared with that between 200 and 240 min (with propranolol). Mean±SEM.

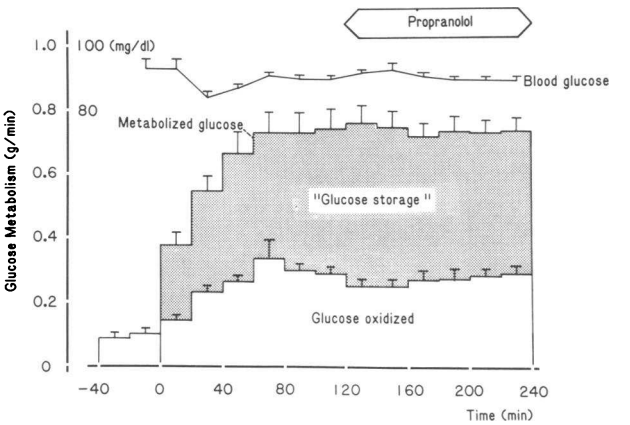

Figure 2. Blood glucose (mg/dl) and the contribution of glucose oxidation and "glucose storage" to the rate of metabolized glucose (g/min) at plasma insulin levels of ~620 μU/ml. The period 80–120 min (without propranolol) was compared with that between 200 and 240 min (with propranolol). Mean±SEM.

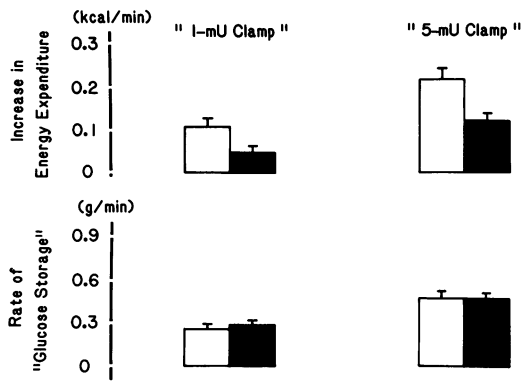

Figure 3. Observed increase in energy expenditure (kcal/min) (*top*) and rate of "glucose storage" (g/min) (*bottom*) before (80–120 min, open columns) and after (200–240 min, black columns) β-receptor blockade with propranolol at plasma insulin levels during the 1 mU/kg·min clamp (~90 μU/ml) and the 5 mU/kg·min clamp (620 μU/ml). Values represent mean±SEM. Energy cost of glucose storage is calculated by dividing the increase in energy expenditure by the rate of glucose storage (see Tables I and II).

lines were compared they were found to be significantly different ($P < 0.005$).

Discussion

It is widely accepted that a proportion of the thermic effect of glucose is due to the energy expended for processing ingested or infused glucose, i.e., "obligatory thermogenesis". However, the mechanisms involved in the energy expended in excess of this obligatory cost, i.e., "regulatory" or "facultative" thermogenesis, are controversial. Various suggestions have included stimulation of the sympathetic nervous system (22, 23), increased sodium pumping (24, 25), increased protein turnover (26), and increased substrate cycling (27).

The present study employed the insulin clamp technique in combination with continuous respiratory exchange measurements and β-adrenergic blockade to investigate the contribution of the sympathetic nervous system to the energy cost of glucose storage during steady state conditions of normoglycemia, hyperinsulinemia, and augmented glucose uptake.

As expected, significant increases were observed in thermogenesis, glucose oxidation, and nonoxidative glucose disposal during steady state conditions of glucose uptake. These increments were comparable with those found in previous studies (22, 23) at similar levels of hyperinsulinemia. After institution of β-adrenergic receptor blockade, significant decreases in metabolic rate occurred, while glucose uptake, oxidation, and nonoxidative glucose disposal remained unchanged in both study 1 and 2, which resulted in significant reductions in the thermic effect of the infused glucose/insulin and in the estimated energy cost of "glucose storage". These findings clearly demonstrate an important β-adrenergically mediated sympathetic nervous component in the thermic effect of glucose and insulin in normal man.

It is possible that the energy cost of de novo lipogenesis, glucose, or glycogen formation from three carbon compounds, increased Na pumping, and protein synthesis could contribute to the observed thermogenesis. However, two recent studies (18, 19) have shown that de novo lipogenesis is a quantitatively unimportant pathway for the disposal of glucose in healthy young men. In the present study, nonprotein respiratory quotients > 1.00 were not observed. Although it is possible that de novo lipogenesis can occur at nonprotein respiratory quotients < 1.00 (18), the fact that lipogenesis is primarily a hepatic process and that during the euglycemic clamp 80–85% of the infused glucose is taken up in peripheral tissue (28) would suggest that the contribution of this process to the energy cost of glucose storage under the conditions of the present study would be negligible.

In depleted muscles, glycogen repletion has been shown to be proportional to the carbohydrate content of subsequent meals (29), and a direct relationship between muscle glycogen synthase activity and the rate of glycogen synthesis during glucose/insulin infusions has been demonstrated (30, 31, 32). In the liver, Bishop et al. (33) have shown by infusing glucose 6-^{14}C with insulin in dogs that almost all of the ^{14}C that was recovered as liver glycogen was in the 6-C position (>90%),

Table IV. Study 2. Blood Parameters during 5 mU/kg·min Insulin Clamp

	Basal (−40–0 min)	*P*	Clamp (80–120 min)	*P*	Clamp plus propranolol (200–240 min)
Insulin (*μU/ml*)	10.1±1.0	0.001	615±29	NS	628±27
C-peptide (*ng/ml*)	1.52±0.08	0.001	0.78±0.09	NS	0.87±0.12
Free fatty acids (*μmol/l*)	427±47	0.001	141±8	NS	136±0.10
Blood urea nitrogen (*mmol/l*)	4.2±0.4	0.005	3.7±0.3	0.005	3.3±0.3
Norepinephrine (*nmol/l*)	1.05±0.16	0.005	1.50±0.26	0.005	1.83±0.30
Epinephrine (*nmol/l*)	0.15±0.02	NS	0.17±0.02	0.005	0.27±0.03

NS, not significant.

*Table V. Comparison between Euglycemic Hyperinsulinemic Clamps at ≃90 μU/ml and ≃620 μU/ml Insulin before and after β-Adrenergic Receptor Blockade with Propranolol (Mean±SEM, N = 8)**

	Hyperinsulinemic clamp			Hyperinsulinemic clamp plus propranolol		
	(≃90 μU/ml)	*P*	≃620 μU/ml	≃90 μU/ml	*P*	≃620 μU/ml
Post-absorptive						
Metabolic rate (*kcal/min*)	1.30±0.06	NS	1.30±0.07			
Carbohydrate oxidation (*g/min*)	0.096±0.017	NS	0.092±0.009			
Lipid oxidation (*g/min*)	0.066±0.005	NS	0.077±0.006			
Insulin clamp						
Metabolic rate (*kcal/min*)	1.39±0.06	0.005	1.51±0.07	1.34±0.05	0.001	1.42±0.06
ΔMetabolic rate (*kcal/min*)	0.10±0.02	0.02	0.20±0.02	0.05±0.01	0.02	0.11±0.02
Glucose uptake (*g/min*)	0.509±0.052	0.001	0.740±0.061	0.553±0.038	0.001	0.747±0.038
Glucose oxidation (*g/min*)	0.262±0.025	NS	0.306±0.016	0.274±0.014	0.05	0.309±0.017
Lipid oxidation (*g/min*)	0.028±0.005	NS	0.026±0.004	0.018±0.003	NS	0.016±0.003
"Glucose storage" (*g/min*)	0.247±0.038	0.001	0.434±0.047	0.279±0.029	0.001	0.438±0.025
Cost of glucose storage (*kcal/g*)	0.50±0.16	NS	0.47±0.04	0.17±0.05	NS	0.26±0.04

* Only eight subjects completed both tests, which explains the slight differences in values reported in this table when compared to Tables I and II.

and more recently Alger et al. (34) have shown, using ^{13}C nuclear magnetic resonance technique, that D(1-^{13}C) glucose given by intubation to rats is converted to 1-^{13}C glycogen in the liver. Both of these studies give evidence against a large contribution of glycogen synthesis from recycled 3-carbon compounds. Recently DeFronzo et al. (35) have demonstrated that nonoxidative glucose disposal can be accounted for by glucose storage in muscle during the euglycemic clamp with insignificant increases in lactate production. If an increase in lactate recycling, protein turnover, or Na pumping, or any combination of these processes occurs during euglycemic clamp

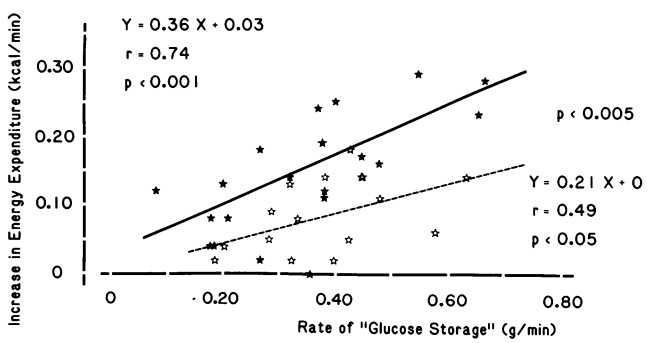

Figure 4. Correlation between the increase in energy expenditure (kcal/min) and the rate of "glucose storage" (g/min) during steady state conditions of hyperinsulinemia (~90 and ~620 μU/ml insulin) and euglycemia, before (⋆) and after (⋆) β-adrenergic receptor blockade with propranolol.

conditions, were to explain some or all of the observed increase in thermogenesis, then it is likely that they are also under the influence of sympathetic control, since almost all of the facultative thermic response could be suppressed by β-adrenergic receptor blockade.

Flatt (21) has calculated the theoretical values for the metabolic cost of processing glucose. Under our conditions of glucose infusion, 5.3% of the glucose energy content is necessary for glucose conversion to glycogen. On the basis of Flatt's value, it was possible to calculate the thermic effect attributable to steady state glucose uptake at each level of hyperinsulinemia (~90 and ~620 μU/ml insulin, Tables I and II). By blocking the sympathetic nervous system, it is possible to reduce the thermic effect of glucose into a range commensurate with that of the metabolic cost of glycogen storage. Using regression analysis, a significant correlation ($r = 0.74$, $P < 0.001$) was found between the increase in metabolic rate and the rate of nonoxidative glucose disposal or "glucose storage" at glucose uptakes ranging from 5.6 to 10.9 mg/kg·min or 0.40–0.78 g/min. The slope of the regression line or the energy cost of "glucose storage" was 0.36 kcal/g, a value similar to that observed by Thiebaud et al. (23). After β-adrenergic receptor blockade, the relationship was less apparent ($r = 0.49$), but it remained statistically significant ($P < 0.05$). However, the slope observed during propranolol infusion (0.21 kcal/g) was significantly lower ($P < 0.005$) than that of the former regression, and was almost identical to the theoretical cost of glucose conversion to, and storage as, glycogen, i.e., 0.20 kcal/g (21).

The present findings are at variance with the report by

DeFronzo et al. (36) in which propranolol was found to reduce insulin/glucose-induced thermogenesis by as much as 70% without any change in nonoxidative glucose uptake. The authors speculate that the decrease in energy expenditure after propranolol may be due to a decrease in insulin-mediated glucose recycling. However, in view of the very small changes in energy expenditure (0.03–0.10 kcal/min) and the fact that experiments with and without propranolol were carried out on different days 1–3 wk apart, we believe that methodological errors and differences in experimental design may help explain the discrepancy between the findings of the present study and that of DeFronzo et al. (36). Finally, it should be emphasized that the current results are supported by our own previous observations that ~30% of the glucose/insulin-induced thermogenesis may be blocked by propranolol under conditions of combined hyperglycemia and hyperinsulinemia (8).

Slight increases in plasma insulin concentrations were observed in both studies throughout the test. From the unchanging C-peptide levels (Tables III and IV) it can be concluded that this was not due to an increase in endogenous insulin secretion. Such increases have been observed before in the presence of increasing glucose uptakes, and have been tentatively ascribed to enhanced tissue sensitivity to the biological effects of insulin with a concomitant decrease in receptor binding during clamp studies of long duration (37).

Glucose uptake did not change significantly before or after propranolol administration in the present study. However, DeFronzo et al. (36) have reported a significant decrease in both glucose uptake and glucose oxidation under similar, but not the same, conditions. This finding is at variance with their previous result that "propranolol alone had no effect on insulin-mediated glucose metabolism" (38). While these differences could be due to the different concentrations of propranolol that were infused, the significant decreases in heart rate that were observed with propranolol in the present study demonstrate that a β-adrenergic receptor blockade was effectively achieved. Moreover, the antecedent diet can substantially influence the metabolic and hormonal responses to a carbohydrate challenge (18). Thus, by performing a single experiment protocol as in the present study, inter-test variability may thus be minimized.

The fact that the energy cost of "glucose storage" was similar at the two different insulin levels in the present study (Table V) does not support the notion that insulin per se exerts a thermogenic effect. However, if we compare the results of the present experiment involving hyperinsulinemia (~620 μU/ml) and normoglycemia with our previous findings under conditions of combined hyperinsulinemia (200 μU/ml) and hyperglycemia (215 mg/dl) (8), the energy cost of "glucose storage" was significantly greater in the present study (0.47±0.04 kcal/g vs. 0.31±0.02 kcal/g, $P < 0.01$). These results might be viewed as favoring a thermogenic role for insulin per se, but we, like Rowe et al. (5), also observed increases in plasma norepinephrine concentrations that tended to be greater during hyperinsulinemia (+0.50±0.12 nmol/l) than during lower levels of insulinemia and hyperglycemia (+0.32±0.08 mmol/l, $P < 0.01$). Thus, it appears more likely that insulin could be a stimulator of sympathetic nervous system activity, possibly via receptors in the ventromedial hypothalamus (39, 40).

While the higher plasma insulin concentration could be criticized as being supraphysiological, it is very interesting to note that the energy costs of "glucose storage" were very similar before β-adrenergic blockade (0.50±0.13 kcal/g and 0.47±0.04 kcal/g) at ~90 μU/ml and ~620 μU/ml insulin, respectively. However, the dispersion was threefold greater at the physiological level, which illustrates that biological and technical variations were more prominent at relatively low rates of glucose uptake. It is suggested that in experiments which investigate the thermic effects of glucose/insulin, one should aim for higher glucose uptakes in order to reduce such pertubations.

A defect in the stimulation of the sympathetic nervous system and brown adipose tissue thermogenesis has been demonstrated in obese animals (41). In man, reduced thermic responses to food (6), norepinephrine (7), and ephedrine (6) have been observed in the obese and in individuals prone to easy weight gain, which suggests that a parallel can be drawn between human and animal obesity. If the findings of the present study are generalized, it is possible to consider the role that a defective sympathetic response to food might play in the etiology of obesity. Dietary-induced thermogenesis is considered to represent 10% of daily energy expenditure, of which stimulation of the sympathetic nervous system could represent 30–50%. Therefore, in absolute terms, the sympathetic nervous system could, at most, account for 3–5% of the total daily energy expenditure, or 75–125 kcal/d (assuming 2,500 kcal/d energy expenditure), provided that it is similarly stimulated by fat and protein ingestion. Since this does not seem to be the case (4), the sympathetic nervous system may contribute no more than 2%, or 50 kcal/d to total daily energy expenditure. While it is tempting to extrapolate such a deficit over one or several years in order to postulate a defective sympathetic response to feeding in the etiology of obesity, it is also possible that other mechanisms, i.e., increased cost of physical activity with a slight increase in body weight, could compensate for this decrease in energy expenditure. Indeed, Welle and Campbell (42) have recently reported that stimulation of the sympathetic nervous system cannot explain the increased thermogenesis that was observed during short-term carbohydrate overfeeding in man. On the other hand, patients who receive prolonged propranolol therapy are not obviously prone to obesity (43), but such observations could be complicated by other treatments for the pathological state, e.g., dietary restriction. For this reason, further studies are necessary to investigate whether some part of the obese population do indeed have a sympathetic nervous system defect and, in addition, if chronic β-blockade in normal subjects under controlled conditions can lead to a gain in body weight.

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