Influence of β-Adrenergic Blockade on Glucose-induced Thermogenesis in Man

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ABSTRACT The role of β-adrenergically mediated sympathetic nervous activity in the regulation of glucose-induced thermogenesis was examined in healthy male subjects. Respiratory gas exchange was measured continuously, using the ventilated hood technique, under conditions of hyperinsulinemia and hyperglycemia (glucose clamp technique, insulin infusion 1 mU/kg per min, glucose levels 125 mg/dl above basal) before and after β-adrenergic blockade (i.v. propranolol, 3-mg bolus plus 0.1 mg/min for 2 h). After 2 h of insulin and glucose infusion in series 1, glucose uptake had increased to 23.5±2.3 mg/kg per min and insulin concentration to 199±21 μU/ml. Simultaneously, the energy expenditure had risen by 0.39±0.05 kcal/min above basal. After propranolol administration, glucose uptake did not change, while energy expenditure fell significantly, to a level 0.28±0.04 kcal/min above basal. The glucose-induced thermogenesis (GIT) was 6.5±0.3% before and 4.6±0.5% ($P < 0.02$) after propranolol. In series 2, insulin and glucose infusion was continued for 4 h without propranolol administration. Glucose uptake rose (+12%) and insulin levels increased (+40%) between the 2nd and 4th h but energy expenditure and GIT remained unchanged. Subjects in series 3 received saline infusion alone for 3 h, at which time propranolol administration as in series 1 was added during a further 2-h period. No changes in energy expenditure were seen during saline or propranolol infusion.

These data demonstrate the presence of a β-adrenergically mediated sympathetic nervous component in glucose-induced thermogenesis in healthy human subjects. This factor may be of importance in the regulation of normal body weight in man.

INTRODUCTION

There is increasing evidence that the sympathetic nervous system is involved in the regulation of dietary-induced thermogenesis (DIT),[1] i.e., the increase in metabolic rate that occurs after food ingestion (1, 2). It has been demonstrated that in the rat, DIT is mediated in part via the sympathetic nervous system, brown adipose tissue being the target tissue mainly responsible for the increased thermogenesis (3). An association between DIT and brown adipose tissue is difficult to assess in man, and the evidence that sympathetic nervous system activity is involved in the regulation of DIT in humans, too, is less compelling. Nevertheless a greater thermic effect has been observed in "energetically-inefficient" individuals, either after ingesting a mixed formula diet or after administration of a sympathomimetic drug, when compared with "energetically-efficient" subjects (4). However, an increase in plasma norepinephrine levels has been shown only after glucose ingestion and not after protein or fat (5), although ingestion of all three foodstuffs is accompanied by significant thermogenic responses. In addition, norepinephrine levels appear to rise more in response to hyperinsulinemia than during hyperglycemia (6).

In spite of the animal experimental data and the indirect evidence in man, a role for the sympathetic nervous system in the regulation of DIT in man remains to be established. An improved understanding of the regulation of DIT in normal man may well be of importance in relation to the pathogenesis of human obesity. Consequently, in this study we have examined

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Received for publication 25 October 1982 and in revised form 16 March 1983.

[1] *Abbreviations used in this paper:* DIT, dietary-induced thermogenesis; GIT, glucose-induced thermogenesis.

the influence of sympathetic nervous system activity on glucose-induced thermogenesis (GIT) during steady state administration of glucose and insulin before as well as after institution of β-adrenergic blockade.

METHODS

Subjects

Nine healthy, male subjects with an average age of 23 yr (range 21–25 yr); height, 181 cm (range 175–192 cm); and weight, 70 kg (range 66–82 kg) volunteered for the study. No subject had a medical history of diabetes mellitus or respiratory ailments and none were taking any medication. All were consuming a weight maintaining diet, which was supplemented with sugared fruit juice for 2 d to ensure that the diet contained at least 250 g carbohydrate. All subjects were informed of the nature, purpose, and possible risks involved in the study before giving their consent to participate. The study protocol had previously been reviewed and 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 to be 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 box heated at 70°C to achieve arterialization of the venous blood. 1 h before the studies started, continuous respiratory exchange measurements were begun and continued for the duration of the experimental protocol. Energy expenditure and substrate utilization were determined by computerized open-circuit indirect calorimetry using the ventilated hood system (7). Three groups were formed from the subjects, one for each of three separate studies (series 1–3), in which each subject served as his own control. Some subjects belonged to more than one group.

Series 1. After 1 h of base-line measurements, seven subjects received a continuous intravenous infusion of insulin (Actrapid, Novo Research Institute, Copenhagen) at a rate of 1 mU/kg per min for 4 h. The blood glucose concentration was raised and maintained at 125 mg/dl above the basal level throughout the study by determining the plasma glucose concentration every 5 min and periodically adjusting an intravenous infusion of glucose solution, using the glucose clamp technique (8). After 2 h of insulin and glucose infusion, a 3-mg bolus of propronolol (Inderal, propranolol hydrochloride, ICI) was administered, followed by infusion of propranolol at 0.1 mg/min together with insulin and glucose for the remaining 2 h of the study.

Series 2. To examine if a spontaneous change in glucose uptake or energy expenditure occurred during the last 2 h of the above study, four subjects repeated the same protocol as in series 1, except that no propranolol was given.

Series 3. To study if an alteration in energy expenditure during the last 2 h of the study period may be due to an effect of propranolol on the resting metabolic rate, four subjects received an intravenous infusion of saline for 5 h. After the third hour, propranolol was administered as in series 1.

Arterialized venous blood samples for the determination of insulin, catecholamines, and blood urea concentration were collected in the basal state and at timed intervals in all three experimental series. Urine was collected during and after each study for determination of glucose and nitrogen content.

Analytical procedures

Plasma and urine glucose were determined in duplicate by the glucose oxidase method on a Beckman glucose analyzer II (Beckman Instruments Inc., Fullerton, CA). Plasma insulin levels were measured by radioimmunoassay (9), catecholamines were analyzed using high performance liquid chromatography technique (10, 11), and blood urea nitrogen was measured using a Technicon autoanalyzer (12). Urinary nitrogen was measured by the Kjeldhal method (13).

Data analysis

Whole body glucose uptake during insulin and glucose infusion was calculated from the rate of glucose infusion required to maintain the predetermined level of hyperglycemia minus the rate of glucose excretion in the urine. For data presentation the mean of the two 20-min periods from 80–120 min and 200–240 min are given.

Energy expenditure and substrate utilization rates were calculated from oxygen consumption, carbon dioxide production, and urinary nitrogen, using the tables of Lusk (14). Correction was applied for changes in the blood urea nitrogen pool. GIT was calculated as the increase in energy expenditure, above basal, expressed as a percentage of the energy content of the glucose metabolized.

Data in the text, tables, and figures are given as mean±SE. Standard statistical methods have been employed, using the paired *t* test, with each subject serving as his own control in series 1–3.

RESULTS

Table I presents average values for the principal results obtained in the basal state and between 80–120 min and 200–240 min in each series. After 2 h of hyperinsulinemia and hyperglycemia in series 1, glucose uptake had risen to 23.5±2.3 mg/kg per min (1.59±0.17 g/min), at which time the insulin concentration had increased from 10.1±1.9 to 200±22 μU/ml and energy expenditure had risen from a basal value of 1.33±0.04 to 1.72±0.07 kcal/min, equivalent to an increase in energy expenditure of 0.39±0.05 kcal/min (Fig. 1). The GIT was 6.5±0.3%.

After propranolol administration in series 1, glucose uptake fell slightly, but not significantly, to 22.5±1.2 mg/kg per min (1.57±0.13 g/min) and insulin rose nonsignificantly to 233±37 μU/ml. However, energy expenditure decreased progressively in all subjects, such that at the end of the 2-h propranolol infusion it had fallen significantly to 1.60±0.07 kcal/min ($P < 0.005$). Thus, during the last 40 min of the propranolol infusion the increase in energy expenditure, above basal, was 0.27±0.04 kcal/min (Fig. 1). The GIT was calculated at 4.6±0.5%, a value significantly lower than that observed before propranolol administration

TABLE I

Glucose Uptake, Energy Expenditure, and Insulin Concentrations in Series 1–3

		1st study period		2nd study period	
	Basal	80–100 min	100–120 min	200–220 min	220–240 min
Series 1 (G, I, P)*					
Glucose concentration (*mg/dl*)	93±2	216±2	215±2	219±2	218±2
Glucose uptake ($mg \cdot kg^{-1} \cdot min^{-1}$)	—	22.2±2.1	23.5±2.3	22.5±2.1	22.5±1.2
Energy expenditure (*kcal/min*)	1.33±0.04	1.72±0.07	1.72±0.07	1.61±0.08‡	1.60±0.07§
Insulin (*μU/ml*)	10.1±1.9	198±20	200±22	236±37	233±37
Norepinephrine (*nmol/liter*)	1.01±0.11	1.25±0.25	1.26±0.22	1.47±0.23‡	1.41±0.22‡
Urea concentration (*mmol/liter*)	5.4±0.3	—	4.4±0.2	—	4.0±0.4
Series 2 (G, I)					
Glucose concentration (*mg/dl*)	95±4	221±2	224±2	222±6	218±4
Glucose uptake ($mg \cdot kg^{-1} \cdot min^{-1}$)	—	19.0±2.9	20.5±3.6	23.3±2.8	23.2±2.8
Energy expenditure (*kcal/min*)	1.30±0.06	1.63±0.13	1.67±0.12	1.71±0.11	1.68±0.09
Insulin (*μU/ml*)	6.4±1.2	140±34	149±40	223±77‡	208±59
Norepinephrine (*nmol/liter*)	1.09±0.20	1.07±0.17	1.07±0.19	1.21±0.21	1.22±0.21
Urea concentration (*mmol/liter*)	5.2±0.7	—	4.5±0.7	—	3.8±0.7
Series 3 (P)					
Glucose concentration (*mg/dl*)	92±2	92±2	92±2	96±3	96±3
Energy expenditure (*kcal/min*)	1.22±0.04	1.28±0.05	1.29±0.08	1.27±0.05	1.25±0.06
Insulin (*μU/ml*)	9.7±1.2	9.6±2.1	9.4±1.8	7.2±1.7	6.9±1.7
Norepinephrine (*nmol/liter*)	0.69±0.10	0.70±0.05	0.70±0.06	0.82±0.06	0.82±0.09

* G indicates glucose infusion; I, insulin infusion; and P, propranolol infusion (120–240 min).

‡ $P < 0.05$ compared with the corresponding value during the first study period (differences caused by random factors).

§ $P < 0.01$ compared with the corresponding value during the first study period (differences caused by random factors).

($P < 0.02$). The blood urea concentration fell progressively throughout the study and had decreased 25% after 240 min.

In series 2, in which the hyperinsulinemic hyperglycemic clamp was continued for 4 h without β-adrenergic receptor blockade, the increase above basal in energy expenditure at 80–120 min was of the same order as in series 1, 0.36±0.07 kcal/min (Fig. 1). At this time, glucose uptake was 20.5±3.6 mg/kg per min (1.41±0.27 g/min), which was not significantly different from the corresponding value in series 1, and the plasma insulin concentration had increased from 6.4±1.2 to 149±40 μU/ml.

After 200–240 min in series 2, plasma insulin had risen to 208±59 μU/ml and glucose uptake had increased significantly to 23.2±2.8 mg/kg per min (1.65±0.24 g/min, $P < 0.001$). However, this value was not significantly greater than that seen during propranolol infusion in series 1. Energy expenditure, instead of falling after 200–240 min as in series 1, continued to rise, such that the increase above basal was 0.41±0.05 kcal/min. The GIT was calculated at 6.8±0.2% and 6.6±0.4% for the period 80–120 and 200–240 min, respectively (NS, Table II). The blood urea concentration fell progressively throughout the study as in series 1 (Table I).

In series 3, in which the subjects received a saline infusion for 3 h and then propranolol for a further 2 h, no significant change in energy expenditure was observed from the basal level, either during the saline infusion or during propranolol administration (Table I).

DISCUSSION

Miller and Mumford (15) suggested that DIT may have two components, specific dynamic action (the thermic effect of food) and "Luxuskonsumption," a phenomenon first described by Neumann (16) to explain the dissipation of energy in order to maintain energy balance. More recently, these two components have been defined (17) as consisting of an obligatory thermogenesis, representing the energy cost of digestion, absorption, and processing or storing of substrates, and a regulatory thermogenesis for the dissipation of energy ingested in excess of the organism's requirements; the latter component corresponding to the concept of "Luxuskonsumption" (16).

This study has investigated the influence upon, and the contribution of the sympathetic nervous system to, the thermogenic effect of intravenous insulin and glucose infusion during steady state conditions of hyper-

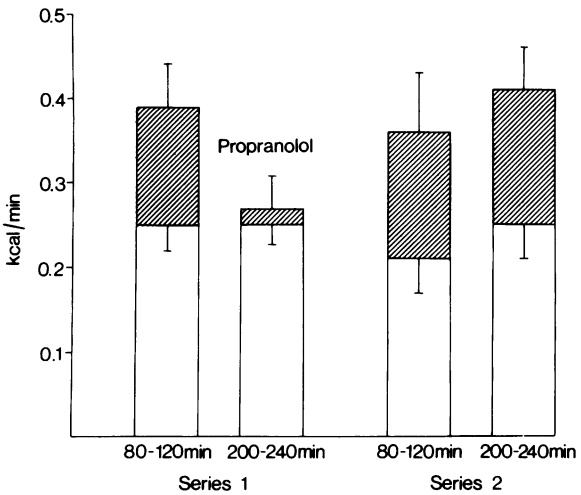

FIGURE 1 Change in energy expenditure (total height of columns) before (80–120 min) and during administration of propranolol (200–240 min) in series 1 are shown to the left ($P < 0.02$). The hatched part of the columns indicates the proportion of the rise in energy expenditure that cannot be accounted for by the estimated energy cost of glucose storage (18) and may represent regulatory as opposed to obligatory thermogenesis (open part of columns) (17). The two columns to the right present the corresponding data for series 2, in which no propranolol was administered (NS). Mean values±SE are indicated.

insulinemia and hyperglycemia before and after β-adrenergic receptor blockade with propranolol. Combined hyperinsulinemia and hyperglycemia were used in order to maximize both glucose storage and the increase in energy expenditure and to minimize the influence of biological and technical variations. As expected, there was a substantial rise in energy expenditure above basal during insulin and glucose administration in series 1. Expressed as a percentage of the potential energy of the metabolized glucose (GIT), this increase amounted to 6.5±0.3% (Table II). During the subsequent propranolol infusion there was a significant fall in energy expenditure, with very little change in the simultaneous glucose oxidation or storage, which caused the GIT to decrease to 4.6±0.5% ($P < 0.02$). In contrast, in series 2, in which no β-adrenergic blockade was instituted, the GIT remained unchanged at a level of 6.6–6.8% throughout the study. Moreover, the findings in series 3 demonstrate that propranolol administration does not significantly influence the basal energy expenditure. Taken together, the findings in series 1–3 provide evidence that the GIT is in part mediated via β-adrenergic sympathetic mechanisms.

The present experimental data on glucose-induced rise in energy expenditure and GIT afford a compar-

TABLE II
Glucose Metabolism as Evaluated from Glucose Uptake and the Respiratory Exchange Ratio in Series 1 and 2

	1st study period 80–120 min	P¶	2nd study period 200–240 min
Series 1 (G, I, P)*‡			
Glucose uptake (*g/min*)	1.59±0.17	—	1.57±0.13
Glucose oxidation (*g/min*)§	0.35±0.03	—	0.33±0.02
Glucose storage (*g/min*)§	1.25±0.14	—	1.24±0.12
Experimentally observed GIT (%)	6.5±0.3	<0.02	4.6±0.5
Theoretically derived GIT (%)‖	4.1±0.10	—	4.2±0.05
Series 2 (G, I)			
Glucose uptake (*g/min*)	1.41±0.27	<0.01	1.65±0.24
Glucose oxidation (*g/min*)§	0.33±0.03	—	0.38±0.03
Glucose storage (*g/min*)§	1.08±0.22	<0.05	1.27±0.21
Experimentally observed GIT (%)	6.8±0.2	—	6.6±0.4
Theoretically derived GIT (%)‖	4.0±0.1	—	4.0±0.1

* Data are given as mean±SE and represent the average values during the last 40 min of each study period.
‡ *G* indicates glucose infusion; *I*, insulin infusion; and *P*, propranolol infusion.
§ Glucose oxidation was estimated on the basis of the nonprotein respiratory exchange ratio (14). Glucose storage was calculated as glucose uptake minus glucose oxidation.
‖ The theoretically derived GIT was calculated using the data on glucose metabolism in the table and the energy cost for each process (22).
¶ *P*-values denote the probability that the differences between the two study periods are caused by random factors.

ison with the corresponding values calculated from the theoretical cost of the glucose storage, which is 5.3% of the energy content of glucose or 0.2 kcal/g (18). The observed rise in energy expenditure as well as the observed GIT are found to be consistently greater (6.5–6.8%) than the corresponding theoretical values (4.0–4.2%) calculated from the estimated cost of the observed glucose metabolism in the present study, except during β-adrenergic blockade (Fig. 1; Table II). The fact that the theoretical GIT is lower than the energy cost of glycogen storage stems from the fact that a proportion of the glucose uptake is directly oxidized to carbon dioxide and water, without significant energetic cost. Thus, the theoretically estimated GIT values above are significantly smaller than those obtained experimentally in series 1 (before propranolol infusion) and in series 2, but the former values are of the same magnitude as that observed during propranolol administration. These findings suggest that ~70% of the thermogenic response to glucose infusion is related to the energy cost of glucose storage, while the remaining 30% is mediated via β-adrenergic sympathetic nervous activity. A 40% rise in plasma norepinephrine levels was seen at 200–240 min in series 1. However, the corresponding increase in series 2 was only 10% (NS), suggesting that the finding in series 1 may reflect a propranolol-induced alteration of norepinephrine (19) rather than increased sympathetic activity.

Two recent studies, using the euglycemic insulin clamp technique and varying rates of insulin infusion (20, 21), have demonstrated that there is a linear relationship between the rise in energy expenditure above basal and the rate of glucose storage. This relationship prevails also under conditions of combined hyperinsulinemia and hyperglycemia (22). In these studies it was noted that the experimentally observed glucose-induced rise in energy expenditure was greater than that calculated from theoretical considerations, thereby confirming the observations of the present study and extending them to a wider and more physiological range.

The current findings suggest that only a very small proportion, if any, of the GIT is likely to be caused by other thermogenic processes, e.g., sodium pumping (23, 24), increased protein turnover (25), or substrate cycles (26), unless they are themselves inhibited by β-receptor blockade or propranolol. The present results are supported by animal experiments demonstrating the occurrence of sympathetically mediated brown adipose tissue thermogenesis in response to both food ingestion and cold exposure in the rat (27, 28). The site of the sympathetically mediated regulatory thermogenesis measured in the present study cannot be determined from the current data. Although there is only suggestive evidence that brown adipose tissue is functional in man (28), it remains a possibility that the observed regulatory thermogenesis did take place in such tissue.

In this context it is of interest that thermoregulatory defects have been observed in genetically obese rodents and that reduced nonshivering thermogenesis has been demonstrated in the genetically obese (ob/ob) mouse (29), suggesting an association between animal obesity and a defect in the sympathetically mediated brown adipose tissue thermogenesis. In man, thermogenesis can be stimulated by intravenous infusion of catecholamines in a manner similar to nonshivering thermogenesis. However, the thermogenic response to norepinephrine is less pronounced in obese subjects than in lean controls (30). Since the current findings indicate that adaptive thermogenesis in man is mediated by the sympathetic nervous system, it may be speculated that a defect in sympathetically mediated thermogenesis may play a role either in the pathogenesis of human obesity or in exacerbating an already existing predisposition towards obesity.

ACKNOWLEDGMENTS

The study was supported by grants from the Zyma Foundation, Nyon, Switzerland, the Nestlé Company, Vevey, Switzerland, the Swedish Medical Research Council (No. 3108) and the Swedish Diabetes Association.

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