Impaired glucose-induced thermogenesis and arterial norepinephrine response persist after weight reduction in obese humans[1–4]

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ABSTRACT A reduced thermic response and an impaired activation of the sympathetic nervous system (SNS) has been reported after oral glucose in human obesity. It is, however, not known whether the reduced SNS activity returns to normal along with weight reduction. The thermic effect of glucose was lower in eight obese patients than in matched control subjects (1.7% vs 9.2%, $p < 0.002$). The increase in arterial norepinephrine after glucose was also blunted in the obese patients. After a 30-kg weight loss their glucose and lipid profiles were markedly improved but the thermic effect of glucose was still lower than that of the control subjects (4.2%, $p < 0.001$). The glucose-induced arterial norepinephrine response remained diminished in the reduced obese patients whereas the changes in plasma epinephrine were similar in all three groups. The results suggest that a defective SNS may be a cause in the development of obesity. *Am J Clin Nutr* 1990;51:331–7.

KEY WORDS Glucose load, obesity, sympathetic nervous system, thermogenesis

Introduction

A number of studies (1–3) showed that obesity is accompanied by a reduced thermic response to glucose and carbohydrate-rich meals. To clarify whether this abnormality is primary or secondary in relation to the obese state, a few studies were conducted in reduced obese and postobese subjects. After weight loss some (4, 5) found that the thermic response to glucose or mixed meals remains decreased whereas others (6) found it further reduced.

The thermic effect of carbohydrate is partly facultative, mediated by the sympathoadrenal system via catecholamines acting on β-adrenoceptors (7–9). A decreased glucose-induced activation of the sympathetic nervous system (SNS) was reported in obese individuals (3) and therefore it is likely that a defective SNS may also be responsible for the reduced glucose-induced thermogenesis in reduced obese patients and contribute to weight regain.

We undertook this study to test whether the reduced thermic effect of ingested glucose and the impaired activation of SNS are improved after a considerable weight loss in obese patients.

Subjects and methods

Subjects

Eight patients were admitted because of severe obesity and were studied under weight-stable conditions before and after a considerable weight loss. The group consisted of seven women and one man; all had a strong family history of obesity. Their age was 32 ± 4 y ($\bar{x}$ ± SEM) and body weight was 122 ± 6 kg. According to medical history, physical examination, electrocardiogram, and blood screening, all were judged to be in good health apart from being obese. All were normotensive with diastolic blood pressures < 90 mm Hg. None were diabetic according to the National Diabetes Data Group criteria (10). Physical characteristics of the patients before and after weight loss are shown in **Table 1**. No information on the body-fat topography was obtained before weight reduction but in the reduced-obese state waist-hip circumference ratio was 0.91 ± 0.08.

The normal-weight–control group consisted of seven healthy subjects (five women and two men) aged 31 ± 5 y, which matched the obese group. Their body weight was 62 ± 3 kg, lean body mass was 47 ± 2 kg, and body fat mass was 15 ± 2 kg. All were normotensive. The body fat content was an estimate obtained from duplicate measurements of the biceps, subscapular, and suprailiac skinfold thicknesses with a Harpenden caliper as described by Durnin and Womersley (11). Lean body mass (LBM) was calculated as body weight minus body fat mass. Percentages overweight were calculated from ideal body

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TABLE 1
Clinical data for obese patients before and after weight reduction*

Patient number	Sex	Age	Body weight		Body fat		LBM		Percentage above ideal weight	
			Before	After	Before	After	Before	After	Before	After
		y	*kg*		*kg*		*kg*		%	
1	M	35	145	87	62	26	83	61	115	43
2	F	38	112	88	49	29	63	59	85	61
3	F	22	123	104	51	39	72	65	74	62
4	F	19	104	92	34	18	70	74	64	48
5	F	30	114	85	50	33	64	52	81	42
6	F	28	123	88	65	ND	58	ND	77	41
7	F	29	153	118	69	ND	84	ND	123	88
8	F	54	104	82	51	30	53	52	76	54
$\bar{x} \pm$ SEM		31.9 ± 3.8	122 ± 6.4	93 ± 4.3	53.9 ± 3.9	28.9 ± 2.9	68.4 ± 3.9	60.5 ± 3.4	86.9 ± 7.4	54.9 ± 5.6

* LBM, lean body mass; and ND, not detected.

weights (12). The participants gave informed consent according to the Helsinki Declaration 2. The protocol was approved by the Municipal Ethical Committee of Copenhagen.

Diet

The thermic effect of glucose was tested before and after weight reduction during weight-stable conditions after a minimum of 5 d of a weight-maintenance diet (35% fat, 50% carbohydrate, and 15% protein) containing ≥ 250 g carbohydrate/d. The lean control subjects followed the same diet but without restrictions in energy intake. The energy restriction for the obese subjects consisted of repeated 8-wk periods on a very-low-calorie diet (VLCD) as the sole source of nutrition. The VLCD (NUPO. Oluf Mørk Bio-Chemic Ltd, Copenhagen) provided 388 kcal/d (1.6 MJ) and satisfied current recommendations regarding protein, vitamins, minerals, and trace elements (13); it was delivered free of charge to the patients. Every 8 wk the VLCD was interrupted by a conventional high-protein, low-fat, and low-carbohydrate diet of 900 kcal (3.8 MJ), which was taken for 2 wk. This alternating diet regimen was continued as long as a substantial weight loss could be obtained, which was 36 wk on average. Subsequently, the energy content of the diet was increased but not so as to allow the body weight to increase. Thus the patients were weight stable for ~5 wk before the test.

Thermic effect of glucose

At 0800 after an overnight fast, an 18-gauge Teflon catheter was placed in the brachial artery for blood sampling and was kept patent with physiological saline. After insertion of the catheter, at least 1 h elapsed before the subjects were studied in the basal state resting supine.

The room temperature was between 23 and 24 °C. Blood samples for determination of substrate and hormone concentrations were collected from the artery at −30, 0, 30, 60, 90, 120, 150, and 180 min relative to the intake of 75 g glucose dissolved in 400 mL of tap water. The subjects breathed through a low-resistance scuba one-way mouthpiece. After 10 min of adaptation, expiratory gas was collected in Douglas bags for 10-min periods before each blood sampling.

Analyses

Glucose in plasma was analyzed by the glucose oxidase method. Plasma was also analyzed for glycerol (14), nonesterified fatty acids (NEFAs) (15), triglycerides (16), and catecholamines (17). Serum immunoreactive insulin, pancreatic glucagon, and C peptide were determined by commercially available radioimmunoassay kits (1).

Expiratory gas was analyzed for oxygen, carbon dioxide, and nitrogen on a mass spectrometer (Centronic 200 MOA, Kjällberg, Stockholm) and volume was measured on a gas meter. The energy expenditure was calculated by the formula described by Bursztein et al (18), which does not require assessment of urinary urea production. This approximation is associated with a relative error of < 1%.

Statistical analysis

All results are presented as means ± SEM. A two-way analysis of variance (ANOVA) for repeated measures was used for testing of statistical significance for an effect of glucose intake, and a modified *t* test was applied to compare two means (19). The response to glucose was estimated separately for each subject as the integrated area of the response curve. Differences in baseline concentrations and in responses to glucose before and after weight loss were tested by a paired *t* test whereas an unpaired *t* test was used when comparisons with the control subjects were performed.

Results

Weight reduction

The physical characteristics of the obese patients before and after weight loss are presented in Table 1. Despite a substantial weight loss of ~30 kg, the patients remained obese as their overweight still exceeded 40% in all cases. Compared with the lean control group the reduced obese subjects still had an in-

creased body weight (93 ± 4 vs 62 ± 3 kg) and LBM (61 ± 3 vs 47 ± 2 kg). Fat accounted for 75% and LBM for 25% of total body weight loss, which reflects the increased LBM in obesity (20).

Glucose tolerance and pancreatic hormones

Both fasting plasma glucose and the total area above basal plasma glucose after ingestion of 75 g glucose were elevated in the obese patients and were reduced to concentrations not significantly different from those of the lean control subjects (**Fig 1 and Table 2**). Although the fasting hyperinsulinemia of the obese subjects was significantly reduced after weight loss ($p < 0.02$), it remained above that of the lean subjects ($p < 0.05$). The insulin area above baseline of the reduced obese subjects was insignificantly reduced compared with pretreatment concentrations and remained insignificantly elevated compared with the lean control subjects. The pattern of C peptide concentrations was similar to that of insulin, ie, baseline concentrations were significantly reduced whereas the response above baseline tended to decrease. Fasting pancreatic glucagon concentration was elevated in the obese patients and normalized with weight reduction. The counterregulatory increase starting ~90 min after glucose ingestion in the lean subjects was still somewhat suppressed in the reduced obese subjects (Fig 1).

Glycerol, nonesterified fatty acids, and triglyceride

The obese patients had significantly higher fasting plasma concentrations of glycerol ($p < 0.00005$), NEFAs ($p < 0.05$), and in the ratio of NEFAs to albumin ($p < 0.04$), which expresses better the free fraction of fatty acids (**Fig 2**). These concentrations were suppressed in response to glucose ingestion, the reduction being more pronounced in obese subjects than in the lean individuals. In reduced obese patients, fasting concentrations as well as the responses to glucose were reduced to concentrations not different from those of the lean control subjects (Fig 2). The fasting triglyceride concentration was significantly reduced from 1.7 ± 0.3 mmol/L in the obese patients to 0.9 ± 0.2 mmol/L after weight reduction ($p < 0.01$), which was not significantly different from the concentration in the lean control subjects (0.6 ± 0.1, NS).

Resting metabolic rate and thermic effect of glucose

Before the ingestion of the 75-g glucose load, resting metabolic rate (RMR) was 5.84 ± 0.24 kJ/min (1.40 ± 0.06 kcal/min) on average in the obese patients (**Fig 3**). After weight reduction RMR decreased to an average of 4.99 ± 0.35 kJ/min (1.19 ± 0.08 kcal/min) ($p < 0.01$), which was indistinguishable from RMR of the lean individuals: 5.06 ± 0.22 kJ/min (1.21 ± 0.05 kcal/min) ($p > 0.5$). The glucose-induced thermogenesis was 1.7 ± 1.2% in the obese patients (Fig 3). This figure was insignificantly improved to 4.2 ± 2.9% ($p = 0.22$) after weight reduction but was still considerably lower than the 9.2 ± 2.4% of the lean subjects ($p < 0.01$).

Catecholamines

The fasting concentrations of arterial norepinephrine (NE) were similar in the obese, in the reduced obese, and in the lean control subjects (**Fig 4**). In the lean subjects, NE increased progressively after glucose ingestion and was still increased 180 min after glucose ($p < 0.0002$). By contrast, in the obese patients NE decreased significantly below baseline concentrations ($p < 0.01$) and returned to slightly above baseline 150–180 min after glucose. After weight reduction NE increased significantly after 30 min ($p < 0.04$) but returned subsequently to baseline concentrations. The integrated response above and below baseline was significantly lower in both the obese (−3 ± 22 nmol·3-h^{-1}·L^{-1}, $p < 0.05$) and the reduced obese (21 ± 11 nmol·3h^{-1}·

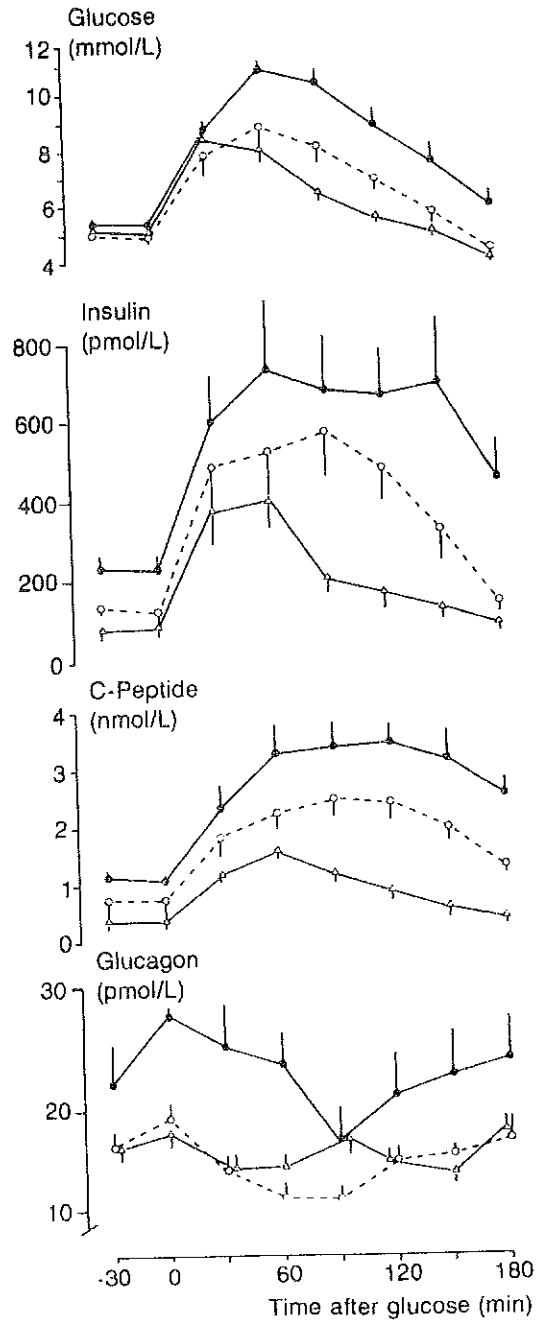

FIG 1. Arterial concentrations of glucose, insulin, C peptide, and glucagon in plasma before and 3 h after ingestion of 75 g glucose. Values are means ± SEM for obese (●), reduced obese (○ and ---), and lean control subjects (△).

TABLE 2
Fasting arterial concentrations and responses of glucose, insulin, C peptide, and glucagon to oral glucose*

Group	Obese	Reduced obese	Lean
Glucose (mmol/L)	5.4 ± 0.2	5.0 ± 0.02†	4.9 ± 0.1
Glucose response ($mmol \cdot L^{-1} \cdot min^{-1}$)	602 ± 42	387 ± 65‡	229 ± 46
Insulin (pmol/L)	235 ± 37	133 ± 17†	72 ± 20†
Insulin response ($nmol \cdot L^{-1} \cdot min^{-1}$)	70 ± 19	55 ± 12	26 ± 6
C peptide (nmol/L)	1.1 ± 0.1	0.8 ± 0.1§	0.4 ± 0.1§
C peptide response ($nmol \cdot L^{-1} \cdot min^{-1}$)	322 ± 48	230 ± 40	107 ± 14†
Glucagon (pmol/L)	26 ± 3.4	18 ± 1.4†	18 ± 1.1

* $\bar{x}$ ± SEM.
† Significantly different from the preceding value, $p < 0.05$.
‡ Significantly different from the preceding value, $p < 0.02$.
§ Significantly different from the preceding value, $p < 0.001$.

L^{-1}, $p < 0.02$) subjects compared with that of the lean subjects (66 ± 12 nmol · 3h/L) but no difference could be found between the obese and the reduced obese. No differences in arterial plasma epinephrine were found between the three groups (Fig 4).

Discussion

Convincing evidence has been presented that body mass and obesity have a strong genetic component (21). According to the laws of thermodynamics, obesity results from an imbalance of energy ingested and energy expended. Recent studies suggest that a low energy expenditure is genetically determined and predisposes to overweight and obesity (22–25). Bogardus et al (22) found that RMR adjusted for differences in LBM, age, and sex was a familial trait; the mean RMR among families varied by ~500 kcal/d but only by ~60 kcal/d within families. In a subsequent prospective follow-up study the same group found a markedly increased risk of becoming obese in subjects with either a low adjusted RMR or a low adjusted 24-h energy expenditure (23). With the doubly labeled water method Roberts et al (24) showed that infants who later became obese had a 21% lower free-living energy expenditure than did other infants at a point when the babies were indistinguishable in regard to body size and fatness. The difference in energy expenditure was sufficient to account for the entire difference in energy deposition (24). These studies have given an impetus to the understanding of overall energy balance in obesity and point to the adjusted RMR as a variable component of 24-h energy expenditure, the nature of which is not fully understood. Apart from RMR the aforementioned studies neither pinpoint other components of energy expenditure nor clarify the pathophysiologic nature of the preobese energy expenditure. Studies of reduced obese with a familial history of obesity may be the first step to identify possible mechanisms. This study reports that a reduced glucose-induced thermogenesis and also an impaired SNS activity persist in reduced obese patients.

The obese patients in this study had a 17% elevation of RMR (Fig 3), which is in accordance with the fact that the increased body mass consists partly of energy requiring LBM (20). After weight reduction they remained ~30 kg heavier than the lean control subjects, and of this overweight ~13 kg was estimated to be excess LBM. Nevertheless, their RMRs were equal to those of the lean control group. Because they were weight stable for ~8 wk and on a weight-maintenance diet containing 250 g carbohydrated for 5 d before the tests, any possible effect of energy restriction can be ruled out. Consequently, these patients can conceivably belong to a subgroup of obese subjects who in the preobese state have a low RMR (24) although it cannot be ruled out that they have adapted to a low energy intake. The variability in RMR may be due to a facultative component of sympathoadrenal origin because some authors (26) found that RMR can be reduced by β-blockade whereas

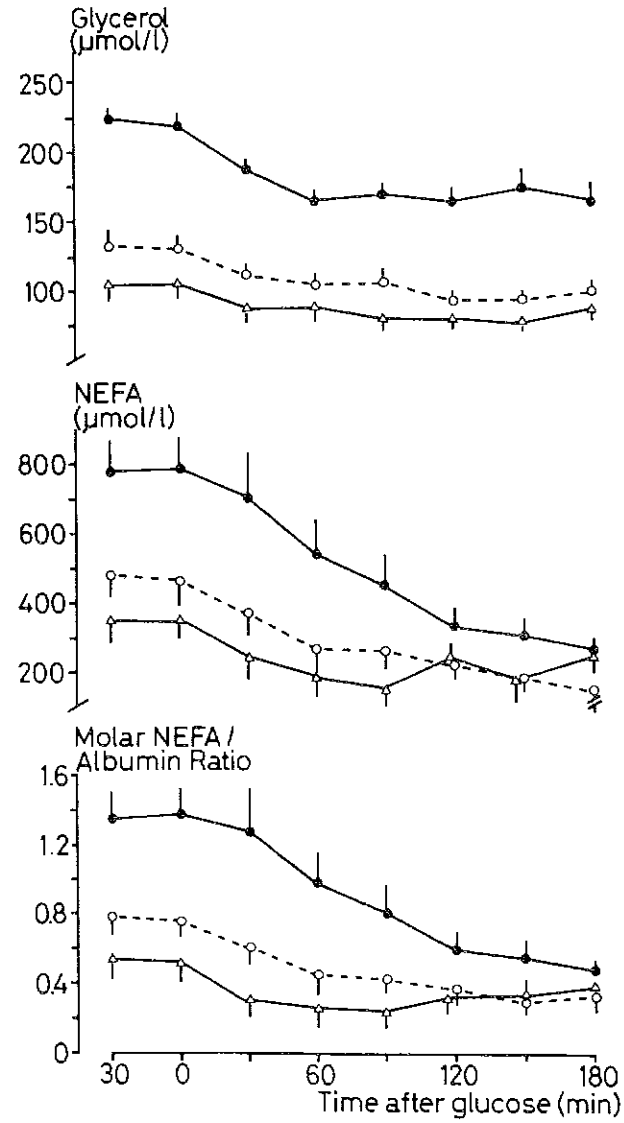

FIG 2. Arterial concentrations of glycerol, nonesterified fatty acids (NEFAs), and the ratio of NEFAs to albumin before and 3 h after ingestion of 75 g glucose. Values are means ± SEM for obese (●), reduced obese (○ and ---), and lean control subjects (△).

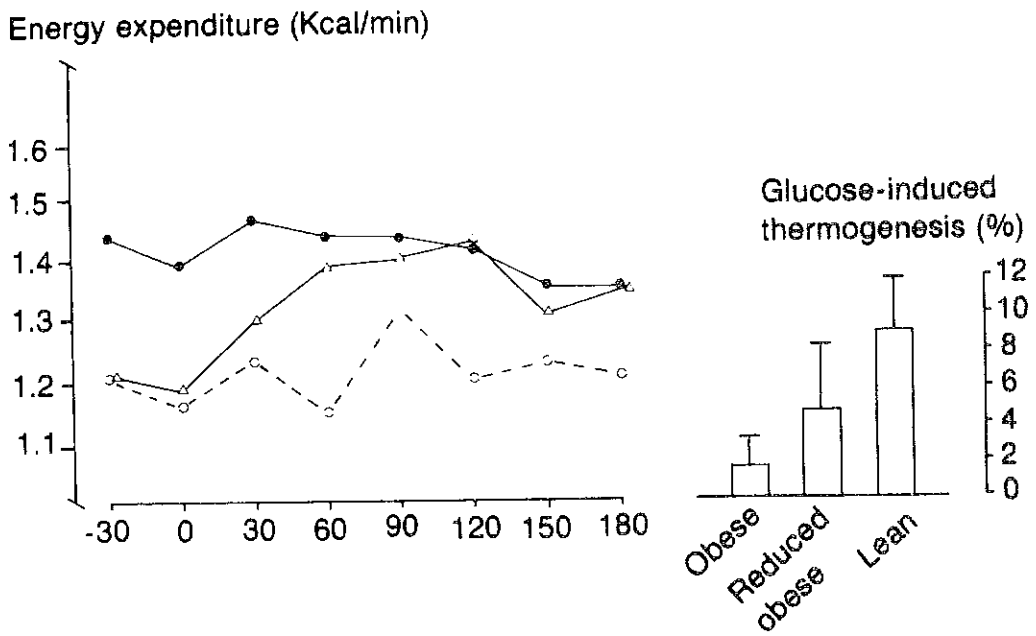

FIG 3. Energy expenditure before and 3 h after ingestion of 75 g glucose. Values are means for obese (●), reduced obese (○ and ---), and lean control subjects (△). In the right figure the bars show the glucose-induced thermogenesis expressed as a percentage of energy content of glucose ingested. Values are means ± SEM.

others have failed (9). These differences may be due to either reduced fasting SNS activity or decreased sensitivity to β-receptor stimulation. In this study baseline NE concentrations did not differ between the obese, the reduced obese, or the lean subjects. Both similar (27) and decreased fasting NE concentrations (28, 29) were reported. Recently, Peterson et al (30) showed convincingly that an increased percentage of body fat is associated with decreased SNS activity, assessed by fasting NE concentrations and other variables reflecting SNS activity (30). A blunted thermogenic sensitivity to catecholamines was also reported (31) in a subgroup of obese patients. This topic requires further clarification.

In the obese patients in this study the glucose-induced thermogenesis was 1.7%, a figure considerably lower than that of the lean control group (9.2%) and also lower than the predicted 5% for obligatory processing. This is a common finding in severely obese patients (3, 4). As shown by Ravussin et al (32), obese patients with marked insulin resistance and impaired glucose tolerance or non-insulin-dependent diabetes mellitus have an energy consuming hepatic gluconeogenesis operating under fasting conditions. This process is suppressed by glucose and insulin, which causes a decrease in energy expenditure. Thus the glucose-induced thermogenesis is the net result of three components: *1*) an obligatory thermogenesis, *2*) a facultative thermogenesis, and *3*) a negative gluconeogeic thermogenesis. Consequently, it is not possible to examine the facultative component in case of a marked fasting hyperglycemia or hyperinsulinemia. In the reduced obese patients, fasting plasma glucose and insulin were significantly reduced and close to normal values (Table 2). Therefore it is likely that the lower glucose-induced thermogenesis of the reduced obese subjects can be attributed to an attenuated facultative component, which is supported by the blunted NE response. We (3) previously reported a defective arterial NE response to oral glucose in severely obese subjects with both normal and impaired glucose tolerance. Other groups (29, 33) found a defective NE responsiveness to hypoglycemia and orthostatic changes in some obese subjects and a lower plasma appearance rate of NE during overeating in obese subjects compared with lean control subjects (34). These studies, however, are not conclusive because the pertubations in SNS activity and in glucose-induced thermogenesis may not necessarily be causative in the development of obesity. They may equally well be consequences of the obese state, ie, the insulin resistance of the receptors mediating the stimulation of SNS. In this study the patients were studied under weight-stable conditions before and after a weight loss of 30 kg. Although the reduced obese patients were still obese, their metabolic profile (glycerol, NEFAs, and glucose tolerance) was markedly improved. However, they still showed a reduced glucose-induced thermogenesis and a blunted response in arterial NE. A number of studies (4–6) reported a reduced thermogenic increase after carbohydrate and mixed meals. However, the SNS activity was not evaluated in these studies. For this purpose plasma concentrations of NE seem sufficient as they reflect changes in SNS activity measured with direct nerve recordings (35). Jung et al (36) reported a blunted NE response to hypoglycemia in formerly obese patients. Our results suggest that the diminished glucose-induced thermogenesis in the obese and reduced obese patients may be due to a diminished or absent facultative thermogenesis caused by a defective SNS activity. This is supported by a recent study by Vernet et al (27) who found β-blockade to reduce the increment in energy expenditure in lean but not in obese patients.

In conclusion, this study demonstrates that severely obese patients after a marked weight loss have a low RMR, a reduced glucose-induced thermogenesis, and defective SNS reactivity.

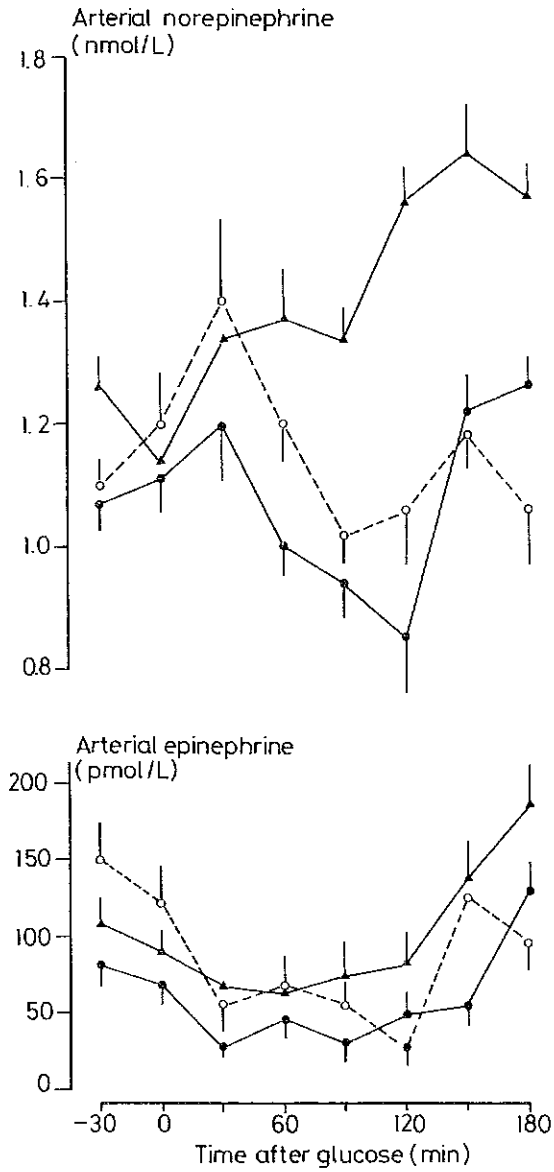

FIG 4. Arterial concentration of norepinephrine and epinephrine in plasma before and 3 h after ingestion of 75 g glucose. Values are means ± SEM for obese (●), reduced obese (O and ---), and lean control subjects (Δ).

These abnormalities point to a central defect and it is conceivable that these abnormalities may cause the development of obesity and promote relapse after weight reduction.

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