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Research Article

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Reduced Sympathetic Nervous Activity

A Potential Mechanism Predisposing to Body Weight Gain

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Abstract

The sympathetic nervous system is recognized to play a role in the etiology of animal and possibly human obesity through its impact on energy expenditure and/or food intake. We, therefore, measured fasting muscle sympathetic nerve activity (MSNA) in the peroneal nerve and its relationship with energy expenditure and body composition in 25 relatively lean Pima Indian males (means \pm SD; 26 \pm 6 yr, 82 \pm 19 kg, 28 \pm 10% body fat) and 19 Caucasian males (29 \pm 5 yr, 81 \pm 13 kg, 24 \pm 9% body fat). 24-h energy expenditure, sleeping metabolic rate, and resting metabolic rate were measured in a respiratory chamber, whereas body composition was estimated by hydrodensitometry.

Pima Indians had lower MSNA than Caucasians (23 \pm 6 vs 33 \pm 10 bursts/min, $P = 0.0007$). MSNA was significantly related to percent body fat in Caucasians ($r = 0.55$, $P = 0.01$) but not in Pimas. MSNA also correlated with energy expenditure adjusted for fat-free mass, fat mass, and age in Caucasians ($r = 0.51$, $P = 0.03$; $r = 0.54$, $P = 0.02$; and $r = 0.53$, $P = 0.02$ for adjusted 24-h energy expenditure, sleeping metabolic rate, and resting metabolic rate, respectively) but not in Pima Indians.

In conclusion, the activity of the sympathetic nervous system is a determinant of energy expenditure in Caucasians. Individuals with low resting MSNA may be at risk for body weight gain resulting from a lower metabolic rate. A low resting MSNA and the lack of impact of MSNA on metabolic rate might play a role in the etiology of obesity in Pima Indians. (*J. Clin. Invest.* 1993. 92:1730–1735.) Key words: sympathetic nervous system • microneurography • body composition • energy expenditure • obesity

Introduction

Reduced sympathetic nervous system activity plays a causative role in several models of obesity in rodents (1). Lesions of the ventromedial hypothalamus resulting in obesity are accompanied by a reduced sympathetic nervous activity, and most forms of genetically inherited obesity in rodents are characterized by decreased sympathetic nervous activity to brown adipose tissue and other peripheral organs (1, 2). These animals

are also characterized by an impaired diet/cold-induced brown adipose tissue thermogenesis (3) and hyperphagia (4, 5), both mechanisms appearing to be related to low sympathetic nervous system activity.

In humans, the role of the sympathetic nervous system in obesity is less clear. Peterson et al. (6) have reported a negative correlation between body fat and plasma norepinephrine levels and suggested that decreased sympathetic activity may be a cause of obesity. The sympathetic nervous system plays a role in regulating energy expenditure in response to glucose/insulin infusions in lean subjects (7). Overfeeding and underfeeding in lean subjects results in significant changes in plasma norepinephrine fluxes paralleling changes in energy expenditure (8), while obese subjects have blunted responses to similar challenges (9). Astrup et al. (10) showed that skeletal muscle appears to be the principal site with respect to the thermogenic effect of sympathomimetic agents in man. Furthermore, Schwartz et al. (11) reported that clonidine, a central sympathetic inhibitory agent, caused a 6% reduction in resting metabolic rate (RMR)¹ and 33% reduction in the thermic effect of a meal. Also, Welle et al. (12) showed that β -adrenoceptor blockade with nadolol decreased RMR significantly by 7% without changes in thyroid hormone levels. Recently, using indirect assessments of sympathetic activity, Saad et al. (13) showed that sympathetic activity was a determinant of energy expenditure in Caucasians but not in Pima Indians, a population with a high prevalence of obesity (14). Food intake seems also to be influenced by the sympathetic nervous system, as indicated by the effect of appetite suppressing sympathomimetics (15).

Thus, there is considerable evidence suggesting that reduced sympathetic nervous system activity may contribute to the pathogenesis of obesity in rodents and growing evidence of its contribution in man. We, therefore, directly measured sympathetic neural outflow to skeletal muscle and its relationship to energy expenditure and body composition in Caucasians compared with Pima Indians.

Methods

Subjects. 25 Pima Indian and 19 Caucasian males were admitted for 5–7 d to the metabolic ward of the Clinical Diabetes and Nutrition Section of the National Institutes of Health (Phoenix, AZ) (Table 1). Women were not studied, in an effort to avoid the confounding effect of change in sympathetic activity during the menstrual cycle (16). All subjects were in good health, as determined from physical examinations and routine blood and urine tests, and they all had normal thyroid

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1. Abbreviations used in this paper: 24hEE, 24-h energy expenditure; MSNA, muscle sympathetic nerve activity; RMR, resting metabolic rate; SMR, sleeping metabolic rate.

Table 1. Physical Characteristics, Metabolic Parameters, and Energy Expenditure in 44 Male Subjects

	Pimas (n = 25)	Caucasians (n = 19)	P
Physical characteristics			
Age (yr)	26±6	29±5	0.10
Weight (kg)	82±19	81±13	0.81
Height (cm)	170±5	177±7	0.0005
Fat-free mass (kg)	58±8	61±7	0.23
Fat mass (kg)	24±13	20±10	0.27
Percent body fat	28±10	24±9	0.17
Waist/thigh ratio	1.62±0.14	1.54±0.15	0.08
Metabolic parameters			
Systolic blood pressure (mmHg)			
	111±7	110±14	0.54
Diastolic blood pressure (mmHg)			
	60±9	58±10	0.52
Heart rate (bpm)			
	59±6	62±9	0.31
24-h Urinary Na excretion (meq/24 h)			
	177±51	188±58	0.51
Fasting plasma insulin (μU/ml)			
	9±5	8±5	0.48
Fasting plasma glucose (mg/dl)			
	93±5	89±4	0.02
Energy expenditure (kcal/d)			
24-h Energy expenditure			
	2289±311	2232±242	0.51
Sleeping energy expenditure			
	1561±202	1581±135	0.71
Resting metabolic rate			
	1817±263	1816±248	0.98

Values are means±SD.

hormone status. None was taking medications. Upon admission, subjects were placed on a weight-maintenance diet of 50% carbohydrate, 30% fat, and 20% protein. Sodium intake ranged from 4 to 6 g/d depending on the weight-maintenance calorie requirement. Non-insulin-dependent diabetes mellitus was excluded by an oral glucose tolerance test performed ≥ 2 d after admission. Body composition was estimated by underwater weighing with simultaneous determination of residual lung volume using the Siri equation for calculation of body fat (17). Circumferences of the waist (at the level of the umbilicus) and thigh (at the gluteal fold) were measured supine and standing, respectively. The

ratio of waist/thigh circumferences is an estimate of the centrality of body fat. The study was approved by the ethics committee of the National Institute of Diabetes and Digestive and Kidney Diseases and by the tribal council of the Gila River Indian Community. Subjects gave written informed consent.

Microneurographic recording. Recordings of muscle sympathetic nerve activity (MSNA) were made in the supine position after an overnight fast, and after ≥ 3 d on the weight-maintenance diet. A tungsten microelectrode (200-μm diam shaft, 1–5-μm noninsulated tip) was inserted into a muscle fascicle of the peroneal nerve posterior to the fibular head. A reference electrode was inserted subcutaneously 1–3 cm from the recording electrode (18). The electrodes were connected to a preamplifier (gain = 1,000) and amplifier (variable gain = 1–99). Neural activity was fed to a band pass filter (band width = 0.7–2.0 kHz) and a resistance-capacitance integrating network (time constant = 0.1 s) to obtain a mean voltage neurogram (Fig. 1). Three criteria were used to indicate acceptable MSNA recordings: (a) electrical stimulation (2–3 V; 0.2 ms, 1 Hz) elicited muscle contraction but not paresthesia in the distal extremity; (b) tapping the skin over the innervated muscle elicited mechanoreceptor discharge, while stroking the skin did not; and (c) the neurogram revealed intermittent bursts that increased during apnea. Evidence that this represents efferent sympathetic nerve activity was derived from earlier studies (18, 19).

Neurograms and electrocardiograms were recorded at 5 mm/s paper speed on a physiological recorder (Windograph, model 40-8474; Gould Inc., Cleveland, OH). Sympathetic bursts were identified by visual inspection and expressed as number of bursts per minute. Intra- (M. Spraul) and interobserver (M. Spraul with E.A. Anderson) variability in scoring muscle sympathetic bursts were determined in six subjects and were low (mean coefficients of variation = 3.8 and 12.1%, respectively). Also, nerve recordings repeated in five subjects on a separate day showed a good intrasubject reproducibility with an intraclass correlation coefficient of 0.90 (mean coefficients of variation = 4.5±3.6%, range 1.0–10.4%), confirming the high intraindividual reproducibility of MSNA (20). In three Pima Indians and seven Caucasians, MSNA was detected but then lost, mostly because of muscle tension, whereas in two Pimas and three Caucasians MSNA could not be detected. These subjects are not included in the analyses. Blood pressure was determined in the right arm by an automatic sphygmomanometer (Sentry model 400; Automated Screening Devices, Costa Mesa, CA). Fasting plasma glucose and insulin levels collected from blood samples before nerve recordings were measured by the glucose oxidase method using a glucose analyzer (Beckman Instruments, Inc., Fullerton, CA) and by radioimmunoassay using a radioassay analyzer (Concept 4; ICN Biomedicals, Costa Mesa, CA), respectively.

Energy expenditure. All measurements of energy expenditure were performed after ≥ 4 d on the weight maintenance diet. 24-h energy

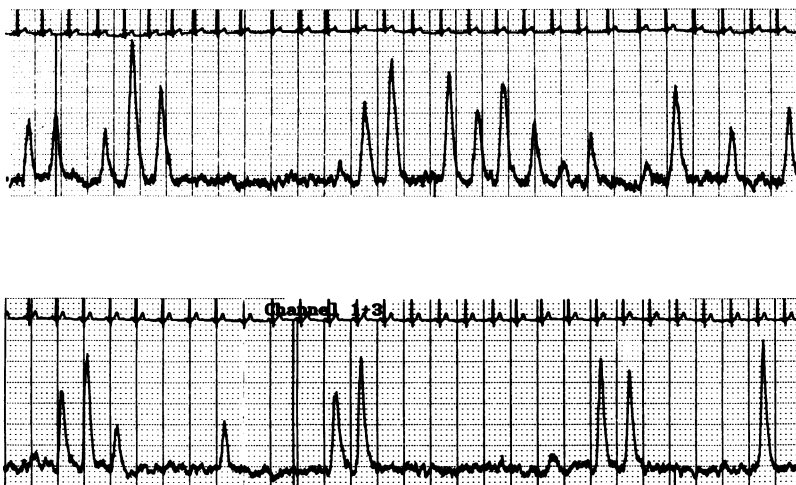


Figure 1. 30-s tracings of integrated neurograms from Pima Indian (lower graph) and Caucasian (upper graph) subjects. Peaks in neurogram indicate multi-fiber bursts of efferent MSNA. Frequency of MSNA was lower in the Pima vs. Caucasian subject (recordings shown approximate the mean frequencies of subjects' respective groups).

expenditure (24hEE) and sleeping metabolic rate (SMR) were measured in an open circuit indirect calorimetry chamber as previously described (21). No exercise was allowed in the chamber, and spontaneous physical activity was monitored by a radar system. The RMR was determined at 0700 h in the chamber using a ventilated hood connected to the same measurement system (21). The subjects were supine and remained motionless and awake during the 21-min test.

Statistical analysis. Baseline MSNA was calculated as the mean of a 10-min period. Statistical analyses were performed by the programs of the SAS Institute (Cary, NC). Since distributions of the continuous variables were not significantly different from normal distributions, parametric statistics were used. Between-group comparisons were made by *t* test for equal or unequal variances. Pearson's correlations were used. Multivariate analyses of covariance were used to test independent effects of covariates such as fat-free mass, body fat, age, waist/thigh ratio, and race (group variable).

Results

Pima Indians and Caucasians were selected to achieve similar means for age and weight. The two groups had a similar mean body fat, fat-free mass, waist/thigh circumference, resting heart rate, blood pressure, and fasting plasma insulin (Table I). Pima Indians had higher fasting glucose levels and were shorter than Caucasians. Sodium excretion measured on the day of MSNA recording was similar in Pima Indians (177 ± 51 meq/d) and Caucasians (188 ± 58 meq/d).

MSNA and physical characteristics. MSNA was lower in Pima Indians compared with Caucasians (23 ± 6 vs 33 ± 10 bursts/min, $P = 0.0007$, Fig. 2). MSNA was significantly correlated with percent body fat, as well as fat mass in Caucasians but not in Pimas (Table II, Fig. 3). In both ethnic groups,

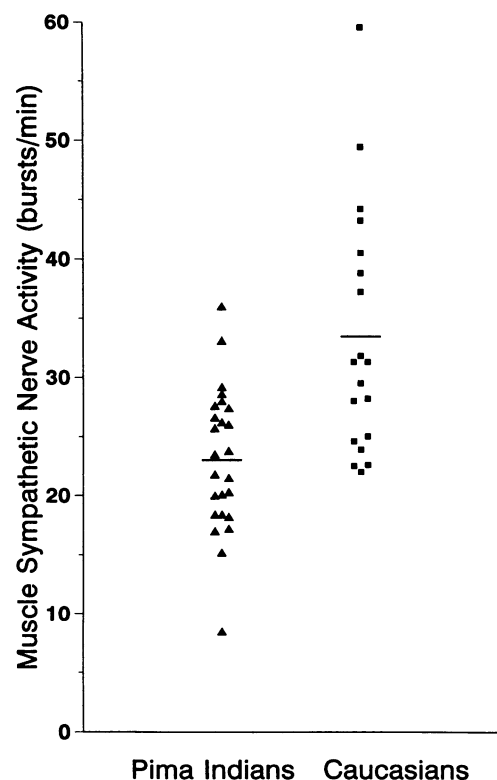


Figure 2. MSNA was lower in Pima Indians compared with Caucasians (23 ± 6 vs 33 ± 10 , $P = 0.0007$ for unequal variances).

Table II. Relationship between Muscle Sympathetic Nerve Activity and Physical Characteristics by Pearson's Correlation

	Pima Indians		Caucasians	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Percent body fat	0.34	0.10	0.55	0.01
Fat mass	0.30	0.15	0.57	0.01
Fat-free mass	-0.02	0.93	0.04	0.87
Age	-0.09	0.65	0.26	0.28

MSNA did not correlate with fat-free mass, age (Table II), blood pressure, heart rate, fasting plasma glucose, or plasma insulin. Age was also not a significant determinant of MSNA independently of differences in percent body fat ($P = 0.73$ and $P = 0.44$ for Pimas and Caucasians, respectively).

MSNA and energy expenditure. Both ethnic groups had similar 24hEE, SMR, and RMR (Table I). This was true even after adjusting energy expenditure for individual differences in fat-free mass, fat mass, and age. Simple correlations showed that all three measurements of energy expenditure (24hEE, SMR, and RMR) adjusted for the above covariates correlated with MSNA in Caucasians but not in Pima Indians (Table III). Similarly, multiple regression revealed that MSNA is a significant independent determinant of energy expenditure in Caucasians but not in Pimas (Table III). The relationships between MSNA and 24hEE adjusted for differences in fat-free mass, fat mass, and age are shown in Fig. 4.

Discussion

The two major findings of this study are (a) muscle sympathetic nerve activity (MSNA) is significantly related to body fatness and energy expenditure in Caucasians, but not in Pima Indians; and (b) Pima Indians have lower fasting MSNA compared with Caucasians of similar age, body weight, and body composition. These results emphasize that part of the variability in metabolic rate among individuals may result from differences in the activity of the sympathetic nervous system. Since a low "relative" resting metabolic rate is a risk factor for body weight gain (22), a low sympathetic activity for a given body size and body composition may favor body weight gain. Also, the low resting MSNA and the lack of effect of MSNA on metabolic rate might play a role in the etiology of obesity in Pima Indians.

Muscle sympathetic nerve activity. MSNA is a measure of sympathetic nervous outflow to the skeletal muscle and represents a direct measurement of sympathetic activity. The sympathetic activity to the muscular bed is similar for different muscle groups, especially at rest (23). It has been shown that MSNA correlates well with indirect measurements of sympathetic nervous system activity such as plasma norepinephrine turnover (24, 25) and plasma norepinephrine levels (20, 26). Although MSNA does not represent "whole body" sympathetic activity (19, 25), skeletal muscle appears to be the principal site for the thermogenic effect of sympathomimetic drugs in man (10) and is a major determinant of the variability in resting energy expenditure (27). Therefore, the muscle sympathetic nerve activity measured in this study is likely to be the branch of the sympathetic nervous system that plays a role in modulating the metabolic rate.

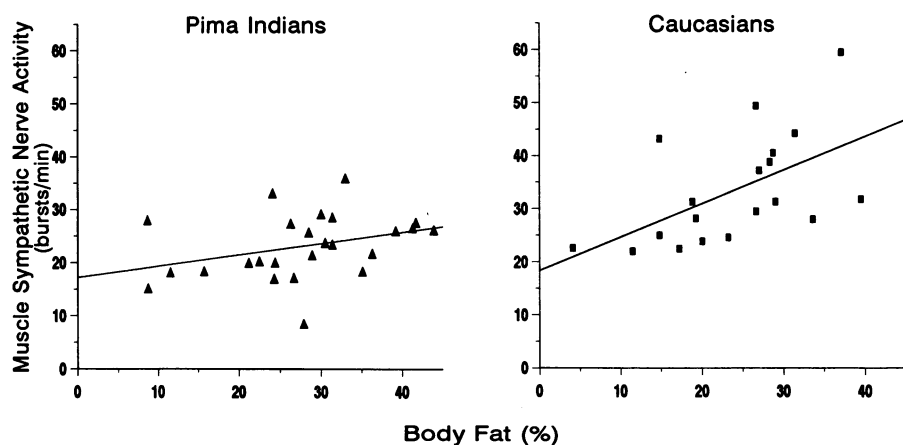


Figure 3. Relationship between MSNA and percent body fat in Pima and Caucasian males. In Caucasians, MSNA correlated significantly with percent body fat (MSNA = 18.4 + 0.63*%body fat; $r = 0.55$, $P = 0.01$) but not in Pima Indians (MSNA = 17.2 + 0.21*%body fat; $r = 0.34$, $P = 0.10$). The slope of the regression line tended to be steeper in Caucasians compared with Pimas (0.63 vs. 0.21 bursts/min per percent of body fat; $P = 0.10$).

The frequency of sympathetic bursts in Caucasians was slightly higher than in many (28–31) but not all (24, 26) published studies. Three factors may contribute to the higher frequency in our study: age and mean body mass index were higher than in most previous studies, and the subjects were kept on a moderately low sodium diet. Sodium intake is a determinant of MSNA with high sodium intake resulting in decreased MSNA (32). The lower MSNA in Pima Indians cannot be attributed to diabetic neuropathy, since diabetes was excluded by an oral glucose tolerance test and subjects had no clinical signs of peripheral neuropathy.

Several studies (26, 28, 29) have shown a positive relationship of MSNA with age. Also, Schwartz et al. (33) reported

significant independent correlations of percent body fat and age with norepinephrine appearance rate. In our study, age does not correlate with MSNA independently of body fat. The small age range and the relatively large range in body fatness in our study may be a reason that we could not confirm the previous studies.

Physiological significance. Rodent models of experimental or genetic obesity are characterized by a reduced central and peripheral sympathetic activity, a low basal and diet-induced energy expenditure (1–3), and increased food intake (4, 5). In humans, changes in plasma norepinephrine turnover have been shown to parallel changes in energy expenditure during fasting or overfeeding in lean (8) but not in obese subjects (9).

Table III. Relationship between Muscle Sympathetic Nerve Activity and Energy Expenditure Adjusted for Differences in Body Weight, Body Composition, and Age

	Pima Indians		Caucasians					
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>				
Simple correlations*								
Adjusted 24hEE	0.11	0.61	0.51	0.03				
Adjusted RMR	0.10	0.63	0.54	0.02				
Adjusted SMR	0.18	0.39	0.53	0.02				
				Equations				
Multiple regression								
Pima Indians	24hEE = 817	+	19.2 FFM ($P = 0.0005$)	+	10.9 FM ($P = 0.002$)	+	4.3 MSNA ($P = 0.47$)	0.77
	RMR = 217	+	25.6 FFM ($P = 0.0001$)	–	3.1 FM ($P = 0.40$)	+	8.1 MSNA ($P = 0.27$)	0.58
	SMR = 368	+	17.0 FFM ($P = 0.0001$)	+	4.6 FM ($P = 0.01$)	+	4.1 MSNA ($P = 0.19$)	0.85
Caucasians	24hEE = 435	+	22.9 FFM ($P = 0.0001$)	+	9.8 FM ($P = 0.004$)	+	6.1 MSNA ($P = 0.04$)	0.86
	RMR = 489	+	14.4 FFM ($P = 0.05$)	+	3.7 FM ($P = 0.51$)	+	11.2 MSNA ($P = 0.05$)	0.51
	SMR = 770	+	8.8 FFM ($P = 0.002$)	+	6.5 FM ($P = 0.003$)	+	4.5 MSNA ($P = 0.02$)	0.81

* Energy expenditure values are adjusted for differences in fat-free mass (FFM), fat mass (FM), and age.

† Variance of the dependent variable accounted for by the predictor variables.

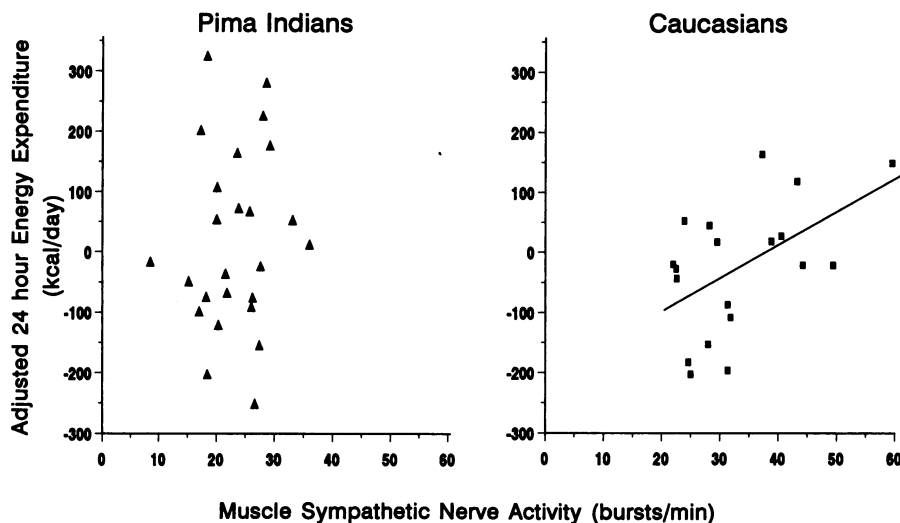


Figure 4. Relationship between MSNA and 24-h energy expenditure adjusted for fat-free mass, fat mass, and age (Pima Indians $r = 0.11$, $P = 0.61$; Caucasians $r = 0.51$, $P = 0.03$).

Resting metabolic rate and the thermic effect of food can be reduced either by β -adrenoceptor blockade (12) or by central blockade of sympathetic nervous system activity by clonidine (11). Since a low resting metabolic rate for a given body size and body composition is a risk factor for body weight gain (22), it is possible that the low metabolic rate associated with a low sympathetic activity would favor body weight gain.

In Pima Indians no correlation was found between MSNA and energy expenditure. Also, despite their lower MSNA, Pima Indians have normal energy expenditure for their fat-free mass, fat mass, and age when compared with Caucasians. This confirms Saad et al. (13) who, by indirect assessments of sympathetic activity, showed that the sympathetic nervous system was a determinant of energy expenditure in Caucasians but not in Pima Indians, despite similar metabolic rates in the two races. Therefore, other mechanisms may increase energy expenditure in adult Pima Indians. Fasting glucose was higher in Pimas suggesting higher rates of gluconeogenesis, an energy costly metabolic pathway (34). This is corroborated by previous studies in which Pima Indians had less suppression of hepatic glucose production during physiologic hyperinsulinemia when compared with Caucasians of similar body composition (35). Insulin resistance in the liver is known to be accompanied by an increase in gluconeogenesis. Other factors, such as substrate cycling (triglyceride/fatty acid cycle, fructose 6-phosphate/fructose 2,6-biphosphate cycle, glucose/glucose 6-phosphate cycle) might be higher in insulin-resistant subjects. All these energy costly processes may explain why a lower energy expenditure was not observed in Pima Indians when compared with Caucasians despite a lower muscle sympathetic nerve activity. However, reduced sympathetic activity may not only promote obesity by its influence on energy expenditure but also by increasing food intake, as experiments in rodents have shown (4, 5).

Hypothesis. Our data contrasts with a report that obesity is associated with lower sympathetic activity (6). However, it is consistent with Landsberg's hypothesis (36) proposing that the increased sympathetic nervous system outflow with percent body fat results from a chronic positive energy balance leading to weight gain. This increase in MSNA seems to stimulate metabolic rate, thereby preventing further weight gain, but may also cause higher blood pressure. Consistent with the hypothesis is

that insulin infusion raises plasma norepinephrine and blood pressure (37), and that moderately obese individuals with mild hypertension have elevated MSNA compared with age-matched lean normotensives (32). Despite a high prevalence of obesity and marked hyperinsulinemia, Pima Indians have a low prevalence of hypertension (38). This low prevalence of hypertension and the lack of impact of the sympathetic nervous system activity on metabolic rate may both result from their low sympathetic activity and possibly a peripheral resistance to sympathetic outflow. In contrast, in obese Caucasians, an elevated sympathetic nervous system activity may result in increases in energy expenditure and arterial blood pressure.

In conclusion, muscle sympathetic nerve activity is positively related to energy expenditure and body fatness in Caucasians. Individuals with low sympathetic outflow may be predisposed to body weight gain and obesity due to a lower metabolic rate. A low resting MSNA and the lack of impact of MSNA on metabolic rate might play a role in the etiology of obesity in Pima Indians.

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