Thermogenesis Induced by a High-Carbohydrate Meal in Fasted Lean and Overweight Young Men: Insulin, Body Fat, and Sympathetic Nervous System Involvement

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OBJECTIVE: This dietary trial was designed to evaluate the effect of an experimental short-term fasting period followed by a high-carbohydrate meal on energy expenditure, thermogenesis, and sympathetic nervous system activity in normal (body mass index < 25 kg/m^2) and overweight (body mass index $>$ 27 kg/m^2) men who were healthy, non-diabetic or with no other endocrine disease, non-smokers, not taking oral prescription medications, and with a stable body weight for the previous 3 mo.

METHODS: Fasting and fed energy expenditures and diet-induced thermogenesis were measured after a high-carbohydrate meal in seven overweight and six lean young male subjects by indirect calorimetry. Heart rate, urinary excretion of catecholamines, serum glucose, and insulin were also measured over the experimental fasting (7.5 h) and postprandial (4 h) periods.

RESULTS: After carbohydrate intake, overweight men showed a significantly higher energy production (kJ/kg of fat-free mass) than did lean individuals, and the diet-induced thermogenesis (percentage of energy intake) was positively correlated with body fat (kg), percentage of body fat, fat-free mass (kg), and fasting pre-meal serum insulin levels. Postprandial cumulative energy expenditure was directly associated with postprandial insulin response and with mean postprandial heart rate values. No significant differences in urinary catecholamines were found between lean and overweight men at basal conditions or during the study period.

CONCLUSIONS: Overweight individuals showed similar short-term sympathetic nervous system responses induced by an experimental fasting period. Although diet-induced thermogenesis after carbohydrate intake was not statistically different between lean and overweight men, the postprandial insulin response and body fat content seemed to be involved in sympathetic nervous system activity. *Nutrition* 2003;19: 25–29. ©Elsevier Science Inc. 2003

KEY WORDS: obesity, carbohydrate-induced thermogenesis, insulin response, sympathetic nervous system activity

INTRODUCTION

Obesity is characterized by excessive fat accumulation related to high energy intake, low energy expenditure, or a mixture of both factors.[1] It has been established that some obese subjects are characterized by a reduced capacity to expend energy, which may be influenced by a genetic trait or environmental factors.[2] Although the mechanisms involved have not been fully established, one contributing agent in this reduced energy expenditure may be impaired sympathetic nervous system (SNS) activity.[3] Hence, obesity may be associated with decreased activity of the SNS or a deficient response to stimuli activating the SNS.[4]

Food intake increases energy expenditure, which has been referred to as diet-induced thermogenesis (DIT) and can be ascribed to obligatory and facultative components. An impairment of DIT in obese patients has been reported by several investigators as a cause of obesity.[5] However, the data are controversial because postprandial thermogenesis also has been found to be similar in lean and obese subjects.[6] In this context, a number of factors have been claimed to influence the facultative component of DIT including glucose tolerance, insulin sensitivity, body fat distribution, and SNS activity.[7,8]

The effect of insulin in thermogenesis is controversial. On the one hand, some studies have shown that thermogenesis is independent of insulin,[9] whereas others have found a contributory role.[10] On the other hand, some investigators have reported that skinfold thickness and body mass index are major predictors of the DIT,[11] whereas others have found that the fat percentage, but not absolute body fat, is related to DIT.[12]

The activity of SNS increases in response to feeding, especially to carbohydrate (CHO) intake, and contributes to the DIT, whereas a reduced SNS tone is a component of the adaptive response to starvation.[4] In this context, the mechanisms involved in the facultative thermogenic response to diet or other stimuli appear to be mediated by catecholamines.[13] Thus, overfeeding and underfeeding in lean subjects result in significant changes in circulating noradrenaline, and the oral ingestion of glucose raises plasma noradrenaline.[4] Nevertheless, the data are contradictory as to whether obese individuals have a blunted activation of SNS after CHO intake.

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TABLE I.

ANTHROPOMETRIC AND BIOCHEMICAL CHARACTERISTICS OF THE 13 STUDY PARTICIPANTS*

	Lean (n = 6)	Overweight (n = 7)
Age (years)	22.1 ± 1.0	20.5 ± 0.6
Height (cm)	174 ± 10	176 ± 10
Body weight (kg)	63.5 ± 2.8	96.1 ± 6.2‡
Body mass index (kg/m^2)	20.8 ± 0.7	30.8 ± 1.7‡
Waist/Hip ratio	0.91 ± 0.05	0.94 ± 0.1
Body fat (% weight)	15.4 ± 1.6	26.7 ± 1.2‡
Body fat (kg)	9.9 ± 1.3	26.1 ± 3.0‡
Fat-free mass (kg)	53.5 ± 2.0	69.9 ± 3.2‡
Basal insulin (μU/ml)	8.8 ± 2.4	13.8 ± 1.3†
Insulin/glucose	1.6 ± 0.4	2.3 ± 0.97
Basal glucose (mmol/L)	5.0 ± 0.1	5.6 ± 0.1
Basal heart rate (beats/min)	52.5 ± 2.7	64.6 ± 3.0†

* Values are shown as mean ± standard error of the mean.
† $P < 0.05$, statistical significance between lean and overweight subjects.
‡ $P < 0.01$, statistical significance between lean and overweight subjects.

Therefore, we investigated SNS activity during a short fasting period and after a high-CHO, low-fat meal in lean and overweight subjects, with a specific focus on CHO-induced thermogenesis and its relation to insulin and different metabolic processes on SNS activity indicators between the two experimental groups.

MATERIALS AND METHODS

Subjects

This study was carried out on 13 young male subjects, six lean (body mass index < 25 kg/m^2) and seven overweight (body mass index > 27 kg/m^2), who were admitted to the Department of Physiology and Nutrition, University of Navarra. All participants were healthy, non-diabetic or with no other endocrine disease, non-smokers, not taking oral prescription medications, and with a stable body weight for the previous 3 mo. The studies were approved by the Clinical Investigation Ethical Committee of Navarra, and informed consent was obtained from all participants according to the Helsinki II declaration. The basal characteristics of the 13 participants are shown in Table I.

Study Procedure

The protocol consisted of a 3-d baseline period followed by the 1-d experiment. During the 3-d baseline period, participants consumed a eucaloric diet designed to maintain body weight, which provided 55% of energy as CHO, 15% as protein, and 30% as fat. The diet was adjusted for their energy requirements, which were based on the Harris-Benedict equation. Subjects recorded all food eaten during the 3-d baseline period with the use of diet diaries, which were analyzed to confirm the amount and composition of energy ingested. Body weights were stable over the 3-d baseline period.

On the experimental day, subjects entered the metabolic unit between 7:30 and 7:45 AM and stayed in until 8:00 PM. After the assessment of body weight, body composition, and the collection of urine samples, participants lied on beds for 30 min until the determination of resting energy expenditure by indirect calorimetry. A venous catheter was inserted into an antecubital vein for blood sampling. All experiments started at 8:00 AM, after an overnight fast of 10 h, and finished at 8:00 PM. Subjects received a test formula meal (between 3:15 and 3:45 PM) after the 7.5-h experimental fasting period, and the postprandial period was studied during the following 4 h. The high-CHO test meal provided 40% of each subject's daily energy requirement, which was assumed to be 1.2 times the resting energy expenditure as measured by indirect calorimetry on the morning of the experimental day. The test meal was a liquid formula (Meritene Polvo, Novartis Nutrition) to which sugar and corn oil were added and provided 80% of energy as CHO (53% as sucrose and 27% as lactose), 17% as protein, and 3% as lipids.

Anthropometry and Body Composition Assessment

Height was measured with a stadiometer to the nearest 1.0 mm and weight to the nearest 100 g with a Seca scale. Using an inelastic tape, waist circumference was assessed at the midpoint between the levels of the lowest rib and the iliac crest, and hip circumference was taken at the level of the greater trochanters. Skinfold thickness was measured at four sites (biceps, triceps, suprailiac, and subscapular) with a Holtain caliper, and the Durnin and Womersley (1974) equation was used to calculate percentage of body fat.[14]

Respiratory Exchange and Heart Rate Measurements

Indirect calorimetry measurements were performed with a continuous open-circuit ventilated-hood system (Deltatrac Monitor MBM-200, Datex-Engstrom Division, Instrumentarium Corp., Helsinki, Finland). A calibration of oxygen, carbon dioxide, and air flow was carried out with reference gas before the beginning of each test. Energy expenditure (EE) was calculated from oxygen consumption, carbon dioxide production (recorded by Deltatrac once per minute and averaged over 20 min), and urinary nitrogen excretion values, according to equations described elsewhere.[15] Fasted measurements were performed at 60-min intervals, beginning after 10 h of fasting (8:00 AM) and were maintained for 7.5 h (17.5 h of fasting). Post-meal measurements were measured at 30-min intervals over the 240 min after CHO intake. Cumulative EE over the experimental fasted and fed periods was calculated as the area under the curve (AUC), taking into account basal and pre-meal fasting values, respectively.[7] DIT was calculated as the increase in EE above pre-meal values for 4 h after meal intake and was expressed as a percentage of energy intake. Heart rate was measured during the indirect calorimetry determinations while subjects were supine with the use of a heart rate monitor, as suggested by the manufacturer (Cardiosport Partner ZW-3, Healthcare Tecnology Limited, UK).

Biochemistry

Subject's blood samples were collected during different times across the trial period (three fasted and four postprandial samples), frozen, centrifuged immediately, and then stored at −40°C before assay. Serum glucose was measured enzymatically (Glucosa PAP, Roche, Spain), and insulin was analyzed by duplicate radioimmunoassay (Coat-A-Count Insulin, Diagnostic Products Corporation, Los Angeles, CA, USA). Urinary concentrations of adrenaline and noradrenaline were measured by high-performance liquid chromatography (Waters, Milford, MA, USA) with a electrochemical detector (ESA, Bedford, MA, USA). Three urine samples were taken with appropriate vials containing 15 mL of 6 N HCl: the first sample was taken the night before the day experiment (after 10-h fasting), the second during the experimental 7.5-h fasted period, and the third during the postprandial period (4 h). Total urine volume was quantified, and samples were frozen at −40°C until assay. The incremental AUCs during fasting and after meal intake

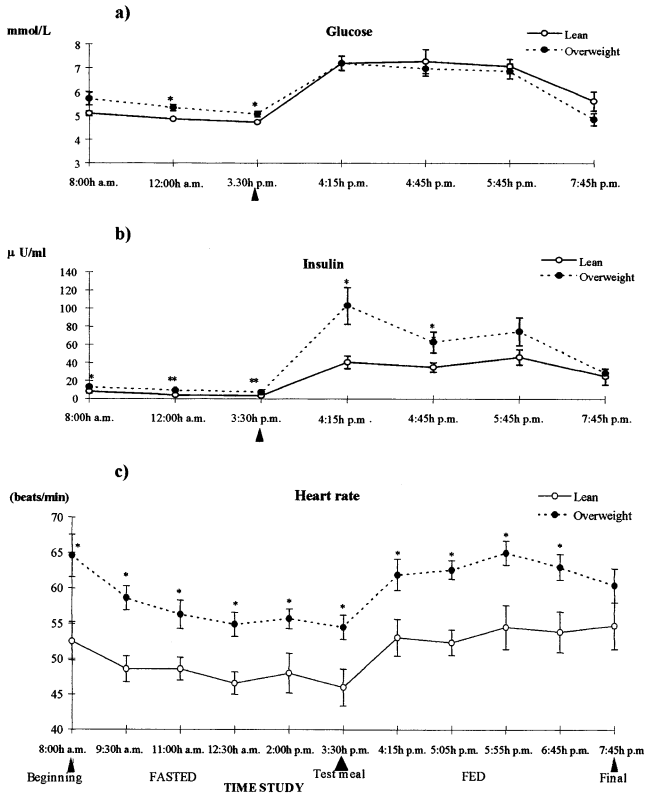

FIG. 1. Time course of serum glucose (a), insulin (b) and heart rate (c) values (means ± SEM) during experimental fasting and after CHO intake. *$P < 0.05$, **$P < 0.01$, statistical significance between lean and overweight men.

were calculated for glucose, insulin, and heart rate according to the trapezoidal method.

Statistical Methods

All results are expressed as mean ± standard error of the mean. The normal distribution of variables was tested, and Tukey's test was used after a two-factor repeated measure analysis of variance for comparison of time-course measurements, with one factor being weight (lean versus overweight) and the other being the repeated time-course variable. Differences between groups in time-point measures were analyzed with Student's *t* test with Bonferroni correction when homoscedasticity criteria were not achieved. Otherwise, Tukey's comparisons were done. Differences between basal, fasted, and fed catecholamine excretion were analyzed with paired *t* test. Other comparisons between groups for table variables were analyzed with Student's *t* test. Relations between variables were evaluated with Pearson's correlation coefficient and stepwise multiple regression. Statistical analysis was performed with SPSS 9.0 software (Microsoft, Redmond, WA, USA) with the help of a statistician.

RESULTS

As expected (Table I), overweight individuals had more body fat and FFM, but no differences were found in body fat distribution between groups. In basal conditions (after a 10-h fasting), overweight subjects showed significantly higher serum insulin concentrations and heart rate values ($P < 0.05$) than did lean men, but there was no statistically significant differences in serum glucose and basal non-protein respiratory quotient (NPQR). The time

TABLE II.

CUMULATIVE FASTED AND FED EE*, DIT AND URINARY EXCRETION OF CATHECOLAMINES†

	Lean (n = 6)	Overweight (n = 7)
Energy expenditure		
Fasted (kJ/kg FFM per 7.5 h)	34.54 ± 0.52	32.69 ± 1.26
Fed (kJ/kg FFM per 4 h)	24.94 ± 0.3	29.88 ± 1.24‡
DIT (% energy intake)	3.56 ± 0.8	6.65 ± 1.2§
Urinary catecholamines		
Adrenaline		
Basal (μg per 10 h)	2.56 ± 0.62	2.96 ± 1.45
Fasting (μg per 7.5 h)	2.24 ± 0.29	3.04 ± 0.19
Fed (μg per 4 h)	2.22 ± 0.34	2.16 ± 0.45
Noradrenaline		
Basal (μg per 10 h)	8.22 ± 1.11	8.28 ± 1.36
Fasting (μg per 7.5 h)	6.75 ± 1.25	8.76 ± 1.11
Fed (μg per 4 h)	6.35 ± 0.92	6.92 ± 0.81

* Calculated as the area under the curve over the 7.5 h of fasting and 4 h after meal intake.
† Values are shown as mean ± standard error of the mean.
‡ $P < 0.05$, statistical significance between lean and overweight subjects.
§ $P = 0.071$, statistical significance between lean and overweight subjects.

course of glucose, insulin, and heart rate values (Fig. 1) indicated that, during the experimental fasting period, overweight as opposed to lean men showed significantly higher insulin serum concentrations (7.6 ± 0.9 versus 3.6 ± 0.2 μU/mL, $P < 0.01$, at 17.5 h of fasting) and significantly higher levels of serum glucose (5.06 ± 0.12 versus 4.72 ± 0.04 mM/L, $P < 0.05$, at 17.5 h of fasting), suggesting a hyperinsulinism pattern. After the high CHO-load intake, both groups showed increased glucose and insulin levels ($P < 0.05$). Total postprandial insulin response (AUC) was higher ($P = 0.07$) in overweight men than in lean men (222.8 ± 42.6 versus 132.2 ± 24.8 μU/mL every 4 h). In addition, there was a significant ($P < 0.05$) group × time interaction concerning insulin response, in which overweight men showed a higher postprandial insulin release than did lean men. No statistically significant differences were found in postprandial glucose response between the overweight and lean groups (5.21 ± 0.96 versus 7.93 ± 1.26 mM/L every 4 h). The mean ratio of insulin to glucose also was significantly higher in the overweight than in the lean men ($P < 0.05$) during the experimental fasting period (1.7 ± 0.2 versus 0.8 ± 0.1) and during the first hour after load intake (8.6 ± 1.2 versus 4.9 ± 0.8).

Heart rate showed a significant decrease ($P < 0.05$) in both groups during the experimental fasting period and was significantly higher in the overweight subjects ($P < 0.05$) during all time-course fasting measurements ($P < 0.05$). Heart rate showed a significant rise ($P < 0.05$) in both groups after CHO intake and was significantly higher in the overweight than in the lean men (61.9 ± 2.2 versus 53.0 ± 2.6 beats/min; $P < 0.05$, at 30 min) until the postprandial 3 h (Figure 1).

The cumulative EE (kJ/kg of FFM) during the experimental 7.5 h of fasting (Table II) indicated no differences between overweight and lean men, while cumulative EE was significantly higher ($P < 0.05$) in overweight than in lean men after CHO intake. Although DIT was higher in overweight subjects, it did not reach statistical significance ($P = 0.07$). However, DIT was positively correlated with pre-meal serum insulin after examining all subjects (Fig. 2a) and each group separately. Also, DIT was associated with percentage of body fat mass ($r = 0.706$, $P = 0.008$), body fat in kilograms ($r = 0.701$, $P = 0.007$), and FFM ($r = 0.625$, $P = 0.022$). The mean NPQR did not differ significantly

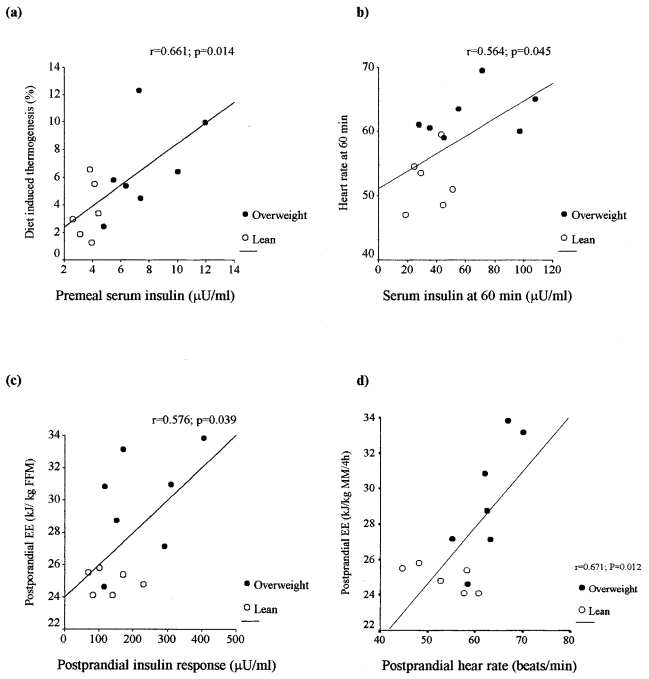

FIG. 2. Associations between DIT and premeal fasting insulin levels (a); heart rate values and serum insulin levels 60 min after CHO intake (b); postprandial cumulative EE and the area under the curve for postprandial insulin response (c); postprandial cumulative EE and postprandial mean heart rate values (d).

between groups during fasting or after meal intake ($P > 0.05$), although it was greater than one in overweight individuals after the CHO load, indicating lipogenesis. Postprandial heart rate values were positively correlated with serum insulin at 30 min ($r = 0.554$, $P = 0.05$) and 60 min ($r = 0.564$, $P = 0.045$) after CHO intake (Fig. 2b). Moreover, postprandial insulin response was positively correlated (Fig. 2c) with total postprandial EE ($r = 0.576$, $P = 0.039$). Also, the postprandial insulin:glucose ratio correlated with postprandial EE ($r = 0.575$, $P = 0.040$), indicating that insulin response was accompanied by higher postprandial EE. In contrast, a stepwise multiple regression that included postprandial metabolic and SNS activity variables produced a positive relation between postprandial EE and mean heart rate values (Fig. 2d), which indicated a strong association between the higher postprandial EE and SNS activity.

There were no significant changes in noradrenaline and adrenaline urinary excretions between basal, experimental fasting, and after CHO intake in lean and overweight men or between lean and overweight subjects during the times studied (Table II).

DISCUSSION

Overweight men presented significantly higher values than did lean men with respect to serum glucose, insulin, and heart rate data during the experimental fasting period (7.5 h), which are major features at the onset of obesity and insulin metabolic syndrome.[8] Because overweight men showed insulin and glucose levels within the normal range, it can be assumed that those individuals showed a hyperinsulinism pattern with a partly reduced insulin sensitivity.

In this study, SNS activity as assessed by heart rate values was significantly lower in lean and overweight subjects during the fasting period, as found by others.[16] However, heart rate variability did not differ between groups as calculated by the fasting AUC, which suggests that the response to fasting was similar in both groups.

Some investigators reported a diminished response of noradrenaline turnover in obese subjects in situations of underfeeding, but differences were not statistically significant when compared with lean subjects.[17] In this trial, SNS activity as assessed by urinary excretion of catecholamines showed no significant differences between lean and overweight men at the basal state or at the end of the short experimental fasting period, which suggests that urinary catecholamines excretion might not reflect short-term SNS activity changes.

After administration of the high-CHO meal, overweight subjects showed a marginally higher DIT, which was associated to a significantly higher cumulative EE (kJ/kg of FFM) than in lean individuals. These data suggest no defect in the thermic response after meal intake, possibly as a defense mechanism among overweight men to prevent further weight gain. Nevertheless, other studies found a defective DIT in obese subjects.[18,19] Moreover, our results confirmed those of other studies[11] by associating DIT with body fat mass in weight and percentage of body weight. We also found a relation between DIT and FFM, which indicates that fat mass and FFM may be predictive variables of the thermic effect of food.[12]

In this trial, fasting serum insulin (before meal intake) was a strong predictor of DIT, which may be due to the fact that insulin increases the facultative component of EE.[9] Thus, insulin directly stimulates SNS,[4] and some investigators[20] have suggested that patients with higher levels of circulating insulin have an increased glucose-induced thermogenesis, which could explain the fact that a high level of fasting insulin attenuates further weight gain.

Insulin response calculated by the incremental AUC after CHO intake was significantly correlated with cumulative EE, whereas serum insulin levels and heart rate values were positively correlated postprandially at 30 and 60 min. In contrast, postprandial EE was strongly associated with postprandial mean heart rate values. Considering these results together, in lean and overweight men, CHO intake may mediate the EE increase by an enhanced SNS activity, and insulin increase may have been involved because insulin directly stimulates SNS activity.[10] However, insulin-induced glucose use increases EE and DIT.[4,8] In this way, the higher postprandial insulin response showed by overweight subjects might explain the higher degree of glucose oxidation and EE,[8] taking into account the slightly higher postprandial NPQR showed by overweight men, indicating a proportionally higher glucose oxidation as compared with lean men. Interestingly, overweight volunteers showed a NPQR above one after receiving the formula, which suggests positive lipogenesis. De novo lipogenesis has a higher energy cost than glucose oxidation,[21] which also may explain the higher EE and DIT in the overweight group. The statistical associations between postprandial insulin, heart rate, EE, and DIT might have been influenced by the fact that lean subjects scored low and overweight men scored high for these variables. Therefore, these data should be interpreted with some caution. Nevertheless, the higher insulin values showed by the overweight group might be implicated in the higher heart rate, DIT, and EE after meal intake.

Although some investigators found a significant positive correlation between heart rate variability and glucose-induced thermogenesis,[7] our data showed no direct relation between heart rate response and DIT. The lack of association in this trial might be explained by the influence of some long-term regulatory factors on heart rate, as has been shown by spectral analysis studies of heart rate and blood pressure variations.[22] However, CHO stimulates SNS, as indicated by the increased urinary noradrenaline excretion after fructose intake.[9] Nevertheless, in our study no marked changes were found between fasting and feeding conditions in lean and overweight men. CHO intake in this study contributed to the increase in the EE and DIT, although urinary noradrenaline excretion remained unchanged. Small changes have been reported in some studies and may not match with the time course of thermogenesis.[23]

The fact that this trial found no direct relation between DIT and urinary noradrenaline, plasma insulin levels, or heart rate values is in agreement with other studies reporting a normal thermic response after glucose ingestion in lean and obese men.[6] In addition, CHO-induced thermogenesis in obese women was not directly correlated with SNS activity as measured by urinary catecholamine excretion.[9]

Reports remain controversial as to whether obese subjects have a blunted activation of the SNS, defective thermogenesis, or other metabolic fuel alterations after CHO intake.[21,24] Nevertheless, these data confirm that insulin plays a role in postprandial EE and SNS activity because it was higher in those overweight individuals with higher levels of serum insulin. Further, the effect of genetic background,[25] which certainly has an important role in the metabolic, hormonal, and SNS responses to dietary intake and measurement conditions (ventilated-hood technique versus respiratory chamber), may explain some of the discrepancies concerning DIT changes in obesity studies.

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