Postprandial sympa tho-adrenal activity: its relation to metabolic and cardiovascular events and to changes in meal frequency

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1. Sympatho-adrenal activity was measured after the consumption of a 3.15 MJ mixed meal. Whole-body noradrenaline spillover rates, forearm plasma noradrenaline spillover and adrenaline secretion rates were derived using isotope dilution methodology. Heart rate and blood pressure spectral analysis measurements were also made. The relation of sympatho-adrenal activity to thermogenic and cardiovascular events was studied. Sympathetic nervous and thermogenic responses were measured for 120 min after the single 3.15 MJ meal and compared with those after three 1.05 MJ meals, given 30 min apart.

2. Whole-body and forearm plasma noradrenaline spillover, and the 0.1 Hz component of systolic pressure power all increased significantly postprandially, while the 0.1 Hz component of heart rate variability, an indirect index of cardiac sympathetic nervous activity, remained unaltered. Adrenaline secretion was unaltered postprandially. Whole-body plasma noradrenaline spillover and thermogenesis during the 120 min postprandial period were 37% and 36% higher after the single meal as compared with the multiple meals, although this was not statistically significant.

3. The sympathetic neural responses were delayed in relation to peak plasma insulin levels and sustained in the face of declining insulin levels. Energy expenditure increased significantly postprandially, but there was no direct quantitative relationship to plasma noradrenaline spillover. Forearm oxygen consumption did not increase postprandially despite significant increases in regional noradrenaline spillover. Thus, no close relation was demonstrated between postprandial sympathetic nervous activation and either insulin secretion or thermogenesis.

INTRODUCTION

The sympathetic nervous system (SNS) plays an important role in the regulation of physiological processes after the ingestion of food. It is responsible for approximately 30% of the thermic effect of food [1, 2] and also helps to maintain blood pressure postprandially [3]. Insulin, which has the ability to activate the SNS [4], is a likely mediator of the postprandial SNS responses.

This study was conducted with two aims in mind. In the first instance, we sought to explore further the nature of sympa tho-adrenal activation after the ingestion of a single large mixed meal, and to determine its relationship to cardiovascular and metabolic events in the first 2 h of the postprandial period. We did this by applying isotope dilution methodology using a dual infusion of radio-labelled noradrenaline (NA) and adrenaline. This allowed us to obtain plasma NA kinetics for the whole body and across the forearm, as well as the secretion rate of adrenaline. We also performed spectral analysis of heart rate and systolic blood pressure variability [5]. These methods allowed us to obtain a composite measure of global sympathetic nervous activation from whole-body NA kinetics, of sympathetic nervous activity across a vascular bed of mostly muscle from forearm NA kinetics, and of indirect indices of cardiac sympathetic and parasympathetic activity and vasomotor sympathetic nervous activity from spectral analysis measurements.

The second aim of the study was to ascertain whether changes in meal frequency were associated with differences in the level of SNS activation. Several studies have addressed the relationship of meal frequency and the thermic effect of food [6–10]. These studies have their basis in earlier reports of an inverse relationship between meal frequency and weight gain [11]. Another issue related to meal frequency is that of postprandial blood pressure control. Alteration in meal frequency and size is a therapeutic recommendation made in cases of postprandial hypotension [3], although the physiological basis for this has been incompletely documented. In investigating the relationship of
Anthropometry

<table>
<thead>
<tr>
<th>Measure</th>
<th>Means ± SEM</th>
<th>Range</th>
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<tbody>
<tr>
<td>Height (cm)</td>
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<td>Weight (kg)</td>
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<td>19.6–26.0</td>
</tr>
<tr>
<td>Percentage fat</td>
<td>16.6 ± 2.0</td>
<td>9.3–26.0</td>
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<tr>
<td>Fat-free mass (kg)</td>
<td>64.0 ± 1.9</td>
<td>52.2–72.8</td>
</tr>
<tr>
<td>Energy intake**</td>
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<td></td>
</tr>
<tr>
<td>Daily intake (MJ/day)</td>
<td>14.5 ± 1.2</td>
<td>11.0–18.8</td>
</tr>
<tr>
<td>Carbohydrate (%)</td>
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<td>35.5–64.2</td>
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<tr>
<td>Fat (%)</td>
<td>32.8 ± 4.5</td>
<td>18.7–49.9</td>
</tr>
<tr>
<td>Protein (%)</td>
<td>20.3 ± 7.4</td>
<td>17.0–35.0</td>
</tr>
</tbody>
</table>

**Complete dietary intakes were obtained only in six subjects.

postprandial thermogenesis and meal frequency, we noted that while in earlier studies, a variety of meal sizes and inter-meal intervals had been employed [6–10], a difference in thermogenesis, when demonstrable, usually became evident during the early postprandial period [9, 10]. Differing levels of sympathetic nervous stimulation with changes in meal frequency might be expected to underlie these differences in thermogenesis.

METHODS

Subjects

Ten healthy, weight-stable males between 19 and 39 years of age were recruited for the study by advertisement. All subjects underwent a detailed clinical examination and routine haematology and biochemistry testing, and were not on any medication at the time of experimentation. None of the subjects were current smokers and all had an alcohol consumption of less than two standard drinks per day. Plasma lipids and electrolytes were within normal ranges for all subjects. An oral glucose tolerance test was also performed to rule out diabetes. Subjects were required to maintain a detailed food intake diary for 3 days (2 weekdays and 1 weekend). The data were then analysed by a trained nutritionist using 'Diet 1', a software package designed for Australian diets. Total daily energy intakes were thus obtained, together with a breakdown of macronutrient composition. Subjects also underwent an anthropometric assessment which included height, weight and skinfold (biceps, triceps, subscapular and suprailiac) measurements. Percentage body fat was then estimated using the age- and gender-specific equations of Durnin and Womersley [12]. The characteristics of the subjects are summarized in Table 1.

Complete details of the experimental procedures were outlined to all participants, and written consent was obtained to the protocol, which was approved by the Ethics Review Committee of the Alfred Hospital.

Study design

General procedure. Experimental testing was performed on 2 days, separated by an interval of approximately 2 weeks. Subjects reported to the laboratory in the morning, 12 to 14 h after their last meal. Alcohol and all beverages except water were prohibited for 12 h before the experiment, and subjects were requested to restrict their physical activity patterns the previous evening to include only light activities. The ambient temperature was maintained between 21 and 23°C.

On the experimental days, subjects consumed either a single large meal (3.15 MJ), or three small meals (1.05 MJ) separated by 30 min intervals. The meals were administered as a standard hospital oral supplement (Ensure Plus, Ross Laboratories, Columbus, OH, U.S.A.), having an energy density of 6.3 kJ/ml and a nutrient composition of 53.3% carbohydrate, 32% fat and 14.7% protein. The order of the experiment (i.e. single large meal or multiple small meals) was randomized in order to exclude an order effect. All measured parameters were monitored postprandially for a duration of 120 min after consumption of the first meal, with the subject in the supine position.

Water control studies. In order to control for temporal effects independent of the consumption of food, three subjects were recalled for a third experimental day, during which water was substituted for the meal. These studies allowed us to determine the coefficients of variation of the various measurement parameters over time.

Measurements of sympathetic nervous activity

Catecholamine kinetics. A dual tracer infusion comprising 3H-labelled l-adrenaline (specific activity 69–78 Ci/mmol) and 3H-labelled l-NA (specific activity 11–25 Ci/mmol; New England Nuclear, Boston, MA, USA) was administered intravenously at 0.8 μCi/min via a dorsal vein in the hand. Arterial blood samples were obtained from a 21G cannula placed percutaneously under local anaesthesia in the brachial artery. The details of the methodology related to the estimation of plasma NA kinetics has been outlined in an earlier methods paper [13] and has since been adapted for the simultaneous examination of plasma NA and adrenaline kinetics [14]. The merits and limitations of this technique of determining catecholamine spillover have been reviewed [15].

Whole-body plasma clearances and rates of spillover of the catecholamines were calculated using the formulae: (i) plasma catecholamine clearance = 3H-labelled catecholamine infusion rate (d.p.m./min)/plasma 3H-labelled catecholamine concentration (d.p.m./ml), and (ii) total catecholamine plasma spillover = 3H-labelled catecholamine infusion rate (d.p.m./min)/plasma catecholamine specific activity (d.p.m./pg).
NA spillover across the forearm was calculated using the following equation [20]:

$$[\text{NA}_a - \text{NA}_v] + (\text{NA}_a \times \text{NA}_{ex}) \times \text{FPF}$$

where $\text{NA}_a$ and $\text{NA}_v$ are the arterial and superficial anteceubital venous concentrations of NA, $\text{NA}_{ex}$ is the fractional extraction of tracer NA across the forearm and FPF is the forearm plasma flow. Forearm blood flow was obtained using the mean of three to five measurements of venous occlusion plethysmography as previously described [16].

Spectral analysis of heart rate and systolic blood pressure variability. The ECG (lead II) and the intra-arterial blood pressure (CMS-327 Disposable Pressure Monitoring Kit; Carlin Medical Supply, Biosensors International Pte Ltd, Singapore) were recorded continuously for a 10 to 12 min period in the basal state and then at 30 min intervals postprandially during the simultaneous measurements of energy expenditure. The data were digitized on-line at 1000 Hz using a 486/50 IBM Compatible PC and a data acquisition package (CVMS; McPherson Scientific, Rosanna, Victoria, Australia) incorporating a 12-bit analogue-to-digital converter (Computer Boards Inc., U.S.A.). The data acquisition system included a threshold peak detection from which the R–R interval and systolic blood pressure were determined. Data segments of 128 s duration were sampled at 2 Hz to create 256-point data sets. For each 10 to 12 min recording, eight data sets of 256 points overlapping by half were processed. The linear trend was removed from each data set to attenuate ‘spectral leakage’. Spectral analysis was performed using a direct Fast Fourier Transform. The frequency resolution was 0.0078 Hz and the highest frequency evaluated was 0.5 Hz. The spectra obtained for the different data sets were averaged to reduce variance and to sharpen reproducible spectral peaks. Power was calculated in two bands. The 0.07–0.14 Hz band is referred to as the 0.25 Hz power or high-frequency power. The clinical application and potential use of this technique has been recently reviewed [17].

Biochemical assays

Catecholamines. Blood samples obtained during the course of the experiment were transferred immediately to ice-chilled tubes containing EGTA and reduced glutathione, centrifuged at 4°C, and the plasma was stored at $-70$°C before assay. Plasma concentrations of NA and adrenaline were determined by HPLC with electrochemical detection. Timed collection of the eluate leaving the detection cell using a fraction collector permitted separation of $^3$H-labelled adrenaline and NA for counting by liquid-scintillation spectrometry. Intra-assay variations were 5.6% for plasma adrenaline at a concentration of 0.27 pmol/ml and 4.5% for plasma NA at a concentration of 0.83 pmol/ml. The intra-assay variations in $^3$H-adrenaline and $^3$H-NA were 3.4 and 7.2% respectively.

Insulin. Arterial blood samples, obtained at the same time points as for catecholamines, were also assayed for serum insulin using a Microparticle Enzyme Immunoassay (Abbot IMx Insulin Assay; Abbott Laboratories, Abbott Park, IL, U.S.A.). The inter-assay coefficients of variation at low (8 m-units/ml), moderate (40 m-units/ml) and high (120 m-units/ml) insulin concentrations were 7.5, 4.7 and 4.1% respectively.

Statistical analysis

All data are expressed as means±SEM. Postprandial changes in the measured parameters were tested for significance using a repeated measures analysis of variance. A paired $t$-test with Bonferroni correction was applied to determine which time points were significant in relation to basal measures.
Differences between the large meal and multiple small meal responses were assessed by determining if there was a significant treatment by time interaction in this within-subject repeated measures design. Data were also analysed by using appropriate summary statistics, as has been recommended for serial measurements [19]. The paired t-test was applied for appropriate summary statistics. All data were analysed using the SYSTAT statistical software programme for the Macintosh, Version 5.2. The null hypothesis was rejected at $P < 0.05$.

RESULTS

Postprandial responses after the ingestion of a 3.15MJ mixed meal

Measures of sympatho-adrenal activation. Whole-body plasma NA spillover rose significantly after consumption of the meal ($P < 0.02$). This amounted to a mean increment of 57% over the entire postprandial measurement period. Postprandial rates of whole-body plasma NA spillover were significantly elevated above baseline values by 60 min, and this elevation was sustained at 120 min. Whole-body plasma NA spillover was unaltered during the water control measurements, the coefficient of variation being 16.7%.

Forearm plasma NA spillover also increased significantly after the meal ($P < 0.05$). The mean postprandial increment was 106% above basal levels. Post-hoc testing revealed that the elevation in forearm plasma NA spillover reached significance only during the latter half of the postprandial measurement period. Whole-body and forearm plasma NA spillover responses are depicted in Fig. 1. Forearm NA spillover was unchanged after the consumption of water, the coefficient of variation being 31%.

The 0.1 Hz power spectrum of systolic blood pressure variability was evaluated as an index of vasomotor sympathetic nervous activity [5]. Repeated measures analysis revealed an increase in the power spectrum over time ($P < 0.05$). Specific time points postprandially were not significantly different from baseline values, although the mean postprandial response constituted a 50% increment (6.0 ± 1.6 compared with 4.0 ± 1.3, $P < 0.01$). These responses and their relationship to postprandial vascular events are shown in Fig. 2. The 0.1 Hz and 0.25 Hz power spectra of heart rate variability were evaluated as indirect measures of sympathetic and parasympathetic components of cardiac nervous activity. While the absolute power of the 0.25 Hz heart rate power spectrum tended to decline postprandially, these changes were not significant. The 0.1 Hz heart rate power spectrum was similarly unchanged (Fig. 3). None of the parameters changed significantly over time after the ingestion of water. The coefficients of variation for the 0.1 Hz component of systolic pressure variability, and the 0.1 and 0.25 Hz components of heart rate variability, were 29.2, 43.7 and 29.2%, respectively.

Adrenaline secretion rate, which was $1.0 ± 0.2$ nmol/min in the resting state, was unaltered postprandially during the 120 min measurement period (mean $0.8 ± 0.1$ nmol/min) (Fig. 4). The coefficient of variation during the water control study was 21.6%.

Serum insulin responses and SNS activity. Serum insulin levels rose significantly postprandially ($P < 0.01$), achieving maximal responses for the group at 30 min. Levels then fell, but were significantly elevated above resting levels at 120 min. The elevation in SNS activity postprandially, as assessed from whole-body and forearm plasma NA spillover...
as well as the 0.1 Hz component of systolic pressure variability, was delayed in relation to the attainment of peak insulin responses, and was sustained in the face of falling insulin levels (Fig. 1). Postprandial serum insulin increments, expressed either as peak levels or as the area under the curve (AUC), were not correlated with either whole-body or forearm plasma NA spillover changes postprandially.

**Thermogenic responses.** These responses are summarized in Fig. 5. There was a significant increase in energy expenditure postprandially \((P < 0.01)\), amounting to a mean increment of 22.2\% above baseline levels. The thermic effect of the meal, which

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**Fig. 1.** Low-frequency (0.1 Hz) systolic pressure power and its relation to postprandial vascular events after the 3.15 MJ meal. Low-frequency systolic pressure power \((P < 0.05)\), forearm blood flow \((P < 0.05)\) and systolic blood pressure \((P < 0.01)\) changed significantly with time. * indicates significance from time '0'. Individual postprandial measurements of forearm blood flow and 0.1 Hz systolic pressure power were not statistically different from basal measurements, although mean postprandial responses were significantly higher than basal measurements for both parameters.

**Fig. 2.** Postprandial heart rate responses to the 3.15 MJ meal (a) and its relationship to the low- (b) and high-frequency (c) components of heart rate variability. There was a significant increase in heart rate postprandially \((P < 0.01, \text{ repeated measures analysis})\). * indicates significance from time '0'. There were no significant changes in either 0.1 Hz (low frequency) or 0.25 Hz (high frequency) heart rate variability over time.

**Fig. 3.** Adrenaline secretion after the consumption of a 3.15 MJ mixed meal. Adrenaline secretion was unchanged during the 120 min postprandial period after the 3.15 MJ meal.
Table 2. Comparison of baseline parameters between the two feeding regimens. Values are means ± SEM. None of the differences were statistically significant using a paired t-test.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Single meal</th>
<th>Multiple meals</th>
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<tbody>
<tr>
<td>Whole-body plasma NA spillover</td>
<td>3.0 ± 0.4</td>
<td>2.4 ± 0.4</td>
</tr>
<tr>
<td>(nmol/min)</td>
<td></td>
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</tr>
<tr>
<td>Forearm plasma NA spillover</td>
<td>0.33 ± 0.1</td>
<td>0.6 ± 0.1</td>
</tr>
<tr>
<td>(pmol min⁻¹ 100 ml⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1 Hz Systolic pressure power</td>
<td>4.0 ± 1.3</td>
<td>3.5 ± 1.3</td>
</tr>
<tr>
<td>(mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Energy expenditure (kJ/min)</td>
<td>6.3 ± 0.2</td>
<td>5.9 ± 0.3</td>
</tr>
</tbody>
</table>

Fig. 5. Thermogenic responses after a 3.15 MJ meal. Whole-body energy expenditure increased significantly (*P < 0.01, repeated measures analysis) after consumption of the 3.15 MJ meal. * indicates significance from time '0'. Forearm oxygen consumption was unaltered postprandially.

Cardiovascular responses. There was a significant increase in heart rate postprandially (*P < 0.01) from 60 min until the end of experimentation at 120 min (Fig. 3). Systolic blood pressure also rose significantly (*P < 0.01), while diastolic blood pressure was unchanged. Evaluation of the water control data suggested that the increase in systolic blood pressure could, in part, be a time-dependent phenomenon, with the three subjects showing small but consistent increases of approximately 5.1% over the 120 min measurement period. Heart rate increments, on the other hand, appeared to be specific to the consumption of food.

Repeated measures analysis revealed that forearm blood flow increased significantly over time (*P < 0.05). None of the postprandial forearm blood flow measurements were significantly different from the basal measure, while overall mean postprandial responses were 61% higher (*P < 0.05). Forearm vascular resistance was unchanged postprandially.

Comparison of sympathetic, insulin and thermogenic responses to three small meals and an isocaloric single large meal. Sympathetic nervous and insulin responses were available on both occasions in nine subjects, while thermogenic responses were available in eight. Baseline measures on the two occasions are shown in Table 2.

The analysis of differences in postprandial SNS activation between the two feeding regimens was confined to those parameters which demonstrated significant changes after the ingestion of the 3.15 MJ meal. Multivariate repeated measures analysis revealed that while there were significant changes over time for whole-body plasma NA spillover (*P < 0.01), forearm plasma NA spillover (*P < 0.05) and the 0.1 Hz component of systolic pressure power (*P < 0.05), there was no significant treatment by time interaction for any of these parameters (Fig. 6). The increment in whole-body plasma NA spillover over the 120 min postprandial duration was 37% higher with the single large meal compared with the multiple small meals, although this was not statistically significant (162.9 ± 24.9 nmol/120 min compared with 118.9 ± 20.9 nmol/120 min, *P = 0.087). A further analysis of the postprandial summary statistics demonstrated that the mean postprandial responses in forearm NA spillover and the 0.1 Hz component of systolic pressure power were not different from baseline after the multiple small meals.

There was a significant increase in serum insulin postprandially (*P < 0.01), with a significant treatment by time interaction (*P < 0.01). Peak insulin levels postprandially were significantly higher for the single large meal compared with the multiple small meals (84 ± 13 m-units/l compared with 62 ± 9 m-units/l, *P < 0.02), although overall differences expressed either as the mean postprandial response or the AUC were not different.

Postprandial thermogenesis rose significantly with time (*P < 0.01) and there was a significant treatment by time interaction (*P < 0.05) (Fig. 7). However, since the resting energy expenditure before the

Fig. 7. Forearm oxygen consumption. Forearm oxygen consumption was unchanged after the consumption of the meal, despite significant elevations in forearm plasma NA spillover.
Whole-body plasma NA spillover was significantly elevated after the consumption of a 3.15 MJ mixed meal and was accompanied by a region-specific significant increase in forearm NA spillover. The low-frequency component of systolic pressure power was also elevated, while the low-frequency component of heart rate variability was unchanged, arguing against postprandial stimulation of the sympathetic nerves of the heart. In an additional study [20], we provided more direct evidence based on cardiac NA spillover measurements from the heart for absence of stimulation of the cardiac sympathetic nerves after a meal. The data thus support the concept of heterogenous sympathetic nervous activation that we have demonstrated in other contexts in humans; for example, sodium depletion targets the renal sympathetic nerves [21]. In contrast, during laboratory mental challenge, cardiac sympathetic nerves are preferentially stimulated [22].

The SNS activation with meal ingestion was delayed in relation to the attainment of peak serum insulin levels, and these elevations in sympathetic nervous activity were sustained in the face of declining insulin levels. This temporal profile is in keeping with the proposed concept of insulin-induced sympathetic activation occurring through a non-vascular compartment, such as the brain [23], and is supported by similar findings during hyperinsulinaemic clamp studies [24, 25]. We were unable to demonstrate a significant correlation between postprandial increments in insulin and sympathetic nervous activity. This may be because of the complex temporal relationship between the two parameters. Alternatively, insulin secretion may not be the prime mover for sympathetic nervous stimulation. The prominent role of insulin in postprandial SNS activation is suggested by studies which have demonstrated increases in plasma NA specifically with carbohydrate meals [26, 27], and by the increases in plasma NA levels [25] and muscle nerve sympathetic activity [24] during hyperinsulinaemic clamp studies. An increase in insulin, however, is not a prerequisite for an increase in postprandial sympathetic activity [28]. It is therefore likely that other factors, including the release of vasodilators from the gut [29] may also play a prominent role in sympathetic nervous activation.

Earlier workers who demonstrated an increase in forearm oxygen uptake after an oral glucose load, discounted a role for NA, since they did not observe an increase in the ‘forearm net release rate’ of NA [30]. Our methodology, which allows for correction of the extraction of NA across the forearm, clearly
demonstrates that forearm plasma NA spillover does in fact increase, but that it is not associated with an increase in forearm oxygen consumption, both measures being derived from the same venous source. Retrograde venous cannulation would have allowed for sampling of relatively uncontaminated skeletal muscle effluent. With our technique, it is likely that some mixing occurred, although the contribution of skin is unlikely to have been large at the forearm blood flows we obtained. Other workers using a mixed meal of approximately similar size and composition were also unable to demonstrate an increase in postprandial forearm oxygen uptake [31]. More recently, other investigators have been unable to demonstrate an increase in skeletal muscle thermogenesis after the infusion of a pharmacological dose of NA [32]. The absence of thermogenesis despite enhanced forearm plasma NA spillover, suggests that the increase in forearm NA spillover in the early postprandial phase serves some other physiological role. The most plausible of these is the maintenance of blood pressure postprandially. This is supported by the concomitant changes in the low-frequency component of the systolic pressure power spectrum. In patients with pure autonomic failure, who have degeneration of sympathetic nerves, postprandial hypotension is both common and severe [3]. The postprandial increase in forearm blood flow we observed despite an increase in regional plasma NA spillover, is consistent with the presence of circulating vasodilators postprandially, including insulin [4].

We were unable to demonstrate any changes in either low- or high-frequency components of heart rate variability that could explain the postprandial increments in heart rate. The high-frequency component of the heart rate power spectrum tended to decrease postprandially, suggestive of a withdrawal of parasympathetic tone to the heart. These changes were not statistically significant however. The absence of changes in the low-frequency component are supportive of our earlier study employing more direct measures of cardiac NA spillover [20], in which we found no evidence of postprandial stimulation of the sympathetic nerves of the heart.

The second aim of the study was to determine whether there were differences in sympathetic nervous activation with changes in meal frequency. Earlier studies which observed higher thermogenic responses with a single large meal compared with multiple small meals [9, 10] explained their results on the basis of higher sympathetic nervous activation with the single large meal, possibly mediated by higher insulin levels. On the other hand, LeBlanc et al. [8] observed a lower thermogenic response with a single large meal compared with multiple small meals, and suggested that this was due to the more frequent cephalic phase sympathetic nervous responses with multiple small meals. None of these studies, however, made any measurements of SNS activity. The view that an infrequent meal pattern leads to obesity suggests that the thermic effect of food eaten with a more frequent meal pattern is higher than that eaten with an infrequent meal pattern. If this were true, postprandial SNS activation would be expected to be higher with a more frequent meal pattern. We were unable to demonstrate any major differences in SNS activation between feeding regimens as assessed by whole-body plasma NA spillover, forearm plasma NA spillover and the low-frequency component of systolic pressure power. Thermogenic responses were also not different between feeding regimens. If anything, both SNS activity and thermogenic responses tended to be lower with increased meal frequency. While we postulated that differences in sympathetic nervous activation related to meal frequency would be evident during the early postprandial period, we did not however follow the responses until they returned to baseline, and the results of this study must be interpreted in this context. The variable results obtained with earlier studies could reflect the considerable differences in study protocols in terms of meal size and inter-meal intervals. From the point of view of blood pressure control, the absence of significant postprandial elevations in forearm plasma NA spillover and the 0.1 Hz component of systolic pressure power with the multiple small meals, suggest that the triggers for sympathetic activation after multiple small meals are less than after an isocaloric single meal. This would provide a physiological basis for recommending that small meals be eaten at frequent intervals in the treatment of postprandial hypotension.

In summary, we have demonstrated that the ingestion of a moderate size, mixed meal is associated with an increase in whole-body and forearm plasma NA spillover during the early postprandial period. From the point of view of meal frequency, we were unable to demonstrate major changes in sympathetic nervous activation during the initial 2 h of the postprandial period. The temporal patterns of insulin and SNS responses do not favour circulating insulin being the direct mediator of postprandial sympathetic nerve activation, but do not exclude continuing insulin activation of the SNS once it has been taken up into a non-vascular compartment like the brain. Increased forearm plasma NA spillover in the early postprandial phase is not associated with an enhanced regional oxygen consumption and probably regulates blood pressure postprandially, a fact consistent with the postprandial increase in the low-frequency component of systolic pressure power. The concomitant increase in forearm blood flow probably reflects vasodilator influences, which are the trigger for reflex sympathetic nervous stimulation.

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REFERENCES


