Blood Pressure Decreases More after High-Carbohydrate Meals Than after High-Protein Meals in Overweight Adults with Elevated Blood Pressure, but There Is No Difference after 4 Weeks of Consuming a Carbohydrate-Rich or Protein-Rich Diet1–4

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Abstract

The replacement of dietary carbohydrates with proteins can lower blood pressure (BP), but the mechanisms remain unclear. This randomized, double-blind, parallel-group study aimed to compare 12-h postprandial sympathetic and hemodynamic responses after high-protein (HP) meals and high-carbohydrate (HC) meals. Fifty-two men and women with untreated elevated BP were tested on d 1 and after 4 wk of supplementation [3 × 20 g protein (HP) or maltodextrin (HC) per day]. No between-group differences were found in postprandial plasma norepinephrine on d 1 and at wk 4. On d 1, postprandial mean arterial pressure (MAP) decreased more in the HC group than in the HP group (P = 0.002). This difference was not present at 4 wk, because the postprandial decline in MAP tended to become larger in the HP group after 4 wk of supplementation (P = 0.07). On both test days, postprandial total peripheral resistance tended to decrease more in the HC group (P < 0.08). After 4 wk of supplementation, cardiac output tended to increase more in the HC group (P = 0.08). In conclusion, ingestion of an HP diet induced a smaller decrease in BP on d 1 than did ingestion of an HC diet. This difference disappeared after 4 wk due to a more pronounced decrease in BP in the HP group after 4 wk than on d 1. These findings cannot explain the BP-lowering effect ascribed to dietary proteins. J. Nutr. 143: 424–429, 2013.

Introduction

The potential of dietary proteins to lower blood pressure (BP)11 could contribute to lifestyle modifications aimed at BP control in (pre)hypertensive patients. Although trials studying the effect of dietary proteins on BP have produced inconsistent results (1–5), the randomized clinical trial on the effects of PROteins on blood PRESsure (PROPRES) has shown that 4 wk of protein supplementation is able to lower BP in overweight men and women with untreated elevated BP as compared with 4 wk of maltodextrin supplementation (6). A subgroup of the PROPRES participants participated in the present substudy addressing possible mechanisms involved in the BP-lowering effect of proteins. High postprandial levels of sympathetic nervous system (SNS) activation may be important in the development of high BP, because chronically elevated SNS

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3 This trial was registered at www.trialregister.nl as NTR1362.

4 Supplemental Figure 1 and Supplemental Tables 1–3 are available from the “Online Supporting Material” link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.

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11 Abbreviations used: BP, blood pressure; CO, cardiac output; DBP, diastolic blood pressure; E, epinephrine; GLP-1, glucagon-like peptide 1; HC, high-carbohydrate; HP, high-protein; HR, heart rate; iAUC, incremental AUC; MAP, mean arterial pressure; MNSA, muscle nerve sympathetic activity; NE, norepinephrine; PROPRES, randomized clinical trial on the effects of PROteins on blood PRESsure; SBP, systolic blood pressure; SNS, sympathetic nervous system; SV, stroke volume; TPR, total peripheral resistance.
activity plays a role in the onset of hypertension in obesity (7). Carbohydrate-supplemented meals may induce greater postprandial SNS activation as a result of a greater postprandial decrease in total peripheral resistance (TPR) compared with protein-supplemented meals. Although the mechanism is not fully known, insulin may be involved in decreasing the TPR (8), and increased SNS activation may be necessary to maintain BP. Few studies compared postprandial hemodynamics of meals with varying macronutrient composition (9–13). These studies reported no differences in postprandial BP responses between high-protein (HP) and high-carbohydrate (HC) meals (9, 11–13) but inconsistent findings with respect to cardiac output (CO) and TPR changes (9, 11).

We hypothesized that the postprandial activation of the SNS would be more pronounced after carbohydrate-supplemented meals, compared with protein-supplemented meals, to compensate for a greater decrease in TPR induced by glucose ingestion. This would result in similar postprandial BP levels after both meals. In addition, we were interested to see whether these responses would persist after consuming a diet high in protein versus a diet high in carbohydrate for 4 wk. The aim of this substudy was to compare changes in SNS activity and postprandial hemodynamics induced by protein- and carbohydrate-enriched meals. Postprandial responses were observed for 12 h (including breakfast, lunch, and dinner) at d 1 and after 4 wk of protein or maltodextrin supplementation in the PROPRES intervention study (6).

Participants and Methods

Experimental design. This study was conducted in a subgroup of participants in the PROPRES study, which compared the effects of 4 wk protein supplementation to 4 wk maltodextrin supplementation on BP in a parallel-group design. A more detailed description of the design of the PROPRES study with inclusion and exclusion criteria can be found elsewhere (6). All PROPRES participants were asked whether they wanted to take part in a substudy in which the postprandial effects of the supplements were investigated on 2 extra test days during the PROPRES intervention. This substudy was powered to significantly show between-group differences of at least 10% with an SD of 15% of group means and was not involved in the measurements. The composition of the supplements can be found in Supplemental Table 2.

SNS activity. SNS activity was estimated by assessment of venous plasma norepinephrine (NE) and epinephrine (E). Venous blood was collected in EDTA-coated vials. Blood was centrifuged at 4°C, 1000 × g for 10 min to acquire plasma, which was stored at −80°C until further analyses. Plasma catecholamines were analyzed by the Dutch Organization for Applied Scientific Research, TNO (16).

Urine was collected before each meal and at the end of the test day. The volume was recorded and aliquots stored at −80°C until further analyses. Urinary catecholamine concentrations were analyzed by liquid chromatography–MS at the University Medical Center Groningen. The amount of E and NE excreted during the first 4 h after each meal was calculated by multiplying urinary concentrations by the volume of excreted urine. The preprandial values from the first urine collection were expressed per mole creatinine excretion because the first urine sample did not represent a standard time period.

BP and heart rate. At each time point, BP and heart rate (HR) were measured twice with a validated automated BP measuring device (OMRON 6 comfort; Omron Healthcare Europe B.V.) in a supine position. The mean was used for further analysis. Mean arterial pressure (MAP) was calculated from SBP and diastolic blood pressure (DBP) with the following formula:

\[
\text{MAP} = \text{DBP} + 1/3 \cdot (\text{SBP} - \text{DBP})
\]

CO, TPR, and stroke volume. CO was measured noninvasively with the Finometer midi and Beatscope easy software (Finapres Medical Systems B.V.) (17). TPR was derived from MAP and CO with the following formula:

\[
\text{TPR} (\text{mm Hg} \cdot \text{min}^{-1} \cdot \text{L}^{-1}) = \frac{\text{MAP}}{\text{CO}}
\]

Stroke volume (SV) was calculated as

\[
\text{SV (mL)} = \text{CO (L \cdot min}^{-1}) \cdot \text{HR (beats \cdot min}^{-1})^{-1} \cdot 10^3
\]

Forearm blood flow. Forearm blood flow (FFB) was measured with venous occlusion strain-gauge plethysmography (Hokanson EC6; Jordan Medical B.V.). During measurement, blood flow through the hand was excluded with a wrist cuff, which was inflated to 220 mm Hg. Means of all measurement cycles were included in analyses if at least 3 cycles were available.

Glucose and insulin. Blood drawn from the antecubital vein was collected in a tube containing sodium fluoride for determination of plasma glucose and in a serum tube for assessment of serum insulin. Blood in the sodium fluoride tube was immediately centrifuged at 4°C, 1000 × g for 10 min, whereas the serum tube was kept at room temperature for 20 min before centrifugation. Plasma and serum were taken and immediately stored at −80°C until analysis. Plasma glucose was analyzed with the glucose/HK assay (Roche Diagnostics), and serum insulin was determined with an electrochemiluminescence immunnoassay (Roche Diagnostics) by MLM Medical Labs (Mönchengladbach, Germany). Serum insulin is expressed in mL/L. Values can be converted to pmol/L by multiplying by 6.945.

Statistical analyses. Baseline characteristics were tested for between-group differences with an independent-samples t test. Between-group differences in weight changes were tested for a group × time interaction by a repeated-measures ANCOVA model. Postprandial data were analyzed by a linear mixed model separately on each test day. The basic model consisted of a random intercept and the following fixed-effects variables: intercept, group, time (as a discrete variable), and the preprandial measurement on that test day. Additional covariates were added to the model one-by-one in the order age, sex, BMI. Covariates with a P value <0.10 based on the likelihood ratio test were kept in the model. The final models are summarized in Supplemental Table 3.

Skewed distributions of FFB, NE, E, and serum insulin were normalized by transformation of these variables to their natural logarithms (ln)
for the statistical analyses. Between-group differences of ln-transformed data are expressed in percentages calculated as \( \% \text{difference} = 100 \left( \frac{e(\text{difference}) - 1}{\text{mean of all Pearson correlation coefficients}} \right) \), where difference is the change in the means of ln-transformed data, i.e., \( \ln(\text{HC group}) - \ln(\text{HP group}) \).

Incremental AUCs (iAUCs) were calculated to test for changes in postprandial responses over 4 wk. Changes in iAUCs were tested by repeated-measures ANOVA.

To test whether the responses of TPR were related to the serum insulin responses, Pearson correlation coefficients between changes in TPR and changes in insulin during the test days were calculated within each participant. Changes were calculated for each subject by subtracting the preprandial value from the individual postprandial values. The mean of all Pearson correlation coefficients was tested for deviation from zero by a 1-sample \( t \) test.

To check whether postprandial responses were significantly changes from the preprandial measurement, the iAUCs were tested for deviations from zero with a 1-sample \( t \) test.

All analyses were performed with SPSS software (version 19.0; IBM). A \( P \) value \(< 0.05 \) was considered to be significant.

### Results

**Participants.** Fifty-six participants were randomly assigned (Supplemental Fig. 1). Three participants in the HP group and 1 in the HC group dropped out after randomization. In the HP group, 1 participant stopped because he felt unwell immediately after consumption of the supplement. One participant started with antihypertensive medication within 1 wk after d 1 of the study, and 1 participant stopped for personal reasons not related to the supplements. Baseline characteristics were comparable between groups (Table 1). Body weight increased by 0.4 \( \pm \) 1.1 kg during the intervention (\( P = 0.002 \)). This change was similar in both groups.

**Meal-induced changes.** iAUCs revealed no significant changes in plasma NE and E, whereas postprandial concentrations of plasma glucose and serum insulin were significantly elevated compared with preprandial concentrations (\( P < 0.001 \)). This was accompanied by a significant postprandial decrease in TPR (\( P < 0.008 \)). The subsequent postprandial decreases in SBP, DBP, and MAP in the HC group, d 1 and wk 4; HP group, only 4 wk; \( P < 0.008 \) were only partly compensated for by the significant postprandial increase in CO (\( P < 0.02 \)). The postprandial increase in CO was mainly due to the increased HR (\( P < 0.001 \)), whereas SV did not change significantly. Postprandial FBF was significantly elevated after HP at 4 wk (\( P < 0.002 \)).

**Differences in meal-induced responses between diet groups on d 1.** Postprandial responses in SNS activity, as reflected by NE concentrations, did not differ significantly between groups on d 1 (Fig. 1A), whereas postprandial plasma E concentrations tended to be 11% lower in the HC group (Fig. 1B; \( P = 0.06 \)). In addition, urinary E excretion tended to be 0.9 \( \pm \) 0.5 nmol \( \cdot \) h\(^{-1} \) lower in the HC group (\( P = 0.09 \)). On d 1, plasma glucose and serum insulin concentrations increased more after the HC meals than after the HP meals (Fig. 1K, L, respectively; \( P < 0.001 \)). The higher serum insulin concentration in the HC group was accompanied by a 1.1 \( \pm \) 0.6 mm Hg \( \cdot \) min\(^{-1} \) larger postprandial reduction in TPR in this group as compared with the HP group (Fig. 1F; \( P = 0.05 \)). Postprandial CO, HR, and SV responses did not differ significantly between groups (Fig. 1G–I, respectively). As a consequence, SBP, DBP, and MAP decreased 3.6 \( \pm \) 1.6, 3.6 \( \pm \) 1.3, and 3.9 \( \pm \) 1.2 mm Hg more in the HC group than in the HP group (Fig. 1C–E, respectively; \( P < 0.03 \)). Postprandial FBF was similar between groups (Fig. 1J).

**Changes in meal-induced responses over the 4-wk intervention period.** Postprandial plasma NE and E did not differ between groups after 4 wk of supplementation (Fig. 2A, B, respectively) nor did the urinary excretions of NE and E. After 4 wk of supplementation, between-group differences in plasma glucose and insulin were maintained (Fig. 2K, L, respectively; \( P < 0.006 \)). TPR tended to decrease 1.0 \( \pm \) 0.5 mm Hg \( \cdot \) min\(^{-1} \) \( \cdot \) L\(^{-1} \) more in the HC group (Fig. 2F; \( P = 0.07 \)). However, after exclusion of 1 outlier with an extremely high fasting TPR in the HP group, TPR decreased significantly more in the HC group compared with the HP group (\( P = 0.01 \)). CO tended to increase 0.4 \( \pm \) 0.2 L \( \cdot \) min\(^{-1} \) more in the HC group (Fig. 2G; \( P = 0.08 \)), although HR and SV did not differ significantly after 4 wk of supplementation (Fig. 2H, I, respectively). Reductions in SBP and MAP were no longer significantly different after 4 wk (Fig. 2C, E, respectively). DBP tended to decrease 2.0 \( \pm \) 1.1 mm Hg more in the HC group (Fig. 2D; \( P = 0.07 \)). Longitudinal analyses of iAUCs revealed a significant between-group difference in the change of the response of SBP over 4 wk and a tendency for different changes in MAP over 4 wk (\( P < 0.06 \)). Disappearance of the difference in SBP and MAP responses between groups appeared to be due to a more pronounced reduction in SBP and MAP after 4 wk of supplementation in the HP group compared with d 1 (\( P = 0.07 \) for both).

**Association between meal-induced TPR and insulin responses.** Because between-group differences in the postprandial insulin response may contribute to the between-group differences in postprandial TPR, correlations between the changes in insulin and changes in TPR were tested. The mean of all individual correlation coefficients (\( r_{\text{mean}} \)) was \(-0.30 \pm 0.05 \) on d 1 and \(-0.39 \pm 0.04 \) after 4 wk (\( P < 0.001 \)).

### Discussion

Contrary to our hypothesis, this study did not show differences in SNS activation between meals supplemented with carbohydrates or proteins, and although the expected larger decrease in
TPR after carbohydrate-supplemented meals was observed, the difference was not significant on either of the test days ($P < 0.08$). A possible contributor to the decrease in TPR is vasodilation in the splanchnic area. This is an acknowledged mechanism for increasing blood flow in this area to facilitate effective nutrient absorption from the gut (11). We hypothesized that TPR would decrease more after HC meals than after HP meals due to the larger insulin response after the carbohydrate-rich meals. Insulin induces NO-dependent vasodilation (8). Our data confirmed the larger decrease in TPR with consumption of the HC diet, although this was not significant on either of the test days ($P < 0.08$), and the inverse association with the insulin response both acutely and after 4 wk.

We further hypothesized that the BP response would be similar after the HC and HP meals. However, BP responses to the HC and HP meals were significantly different on d 1. We found that meal ingestion reduced SBP, DBP, and MAP, with a significantly greater reduction in the HC group. Apparently, the postprandial decrease in TPR was only partly compensated for by an increase in CO, resulting in a net decrease in BP in both

**FIGURE 1** Twelve-hour postprandial changes in plasma NE (A), plasma E (B), SBP (C), DBP (D), MAP (E), TPR (F), CO (G), HR (H), SV (I), FBF (J), plasma glucose (K), and serum insulin (L) after high-carbohydrate and high-protein meals on d 1 of supplementation. Vertical lines indicate breakfast, lunch, and dinner. Values are mean ± SEM, $n = 48–52$. The exact $n$ for each test is mentioned in Supplemental Table 3. *$P < 0.05$ for the whole 12-h period according to the mixed model. CO, cardiac output; DBP, diastolic blood pressure; FBF, forearm blood flow; E, plasma epinephrine; HC, high-carbohydrate group; HP, high-protein group; HR, heart rate; MAP, mean arterial pressure; NE, plasma norepinephrine; SBP, systolic blood pressure; SV, stroke volume; TPR, total peripheral resistance. Serum insulin is expressed in mU·L$^{-1}$. Values can be converted to pmol·L$^{-1}$ by multiplying by 6.945.
groups. The larger BP reduction in the HC group on d 1 could imply a less efficient baroreflex after the HC meals compared with the HP meals. This is in agreement with the finding that cardiac baroreflex sensitivity was reduced in middle-aged men and women with central obesity after a 75-g glucose load (18). However, it is in contrast with the finding that insulin increases baroreflex sensitivity in young men (19). Reduced baroreflex sensitivity may be a characteristic of our relatively old participants. A recently published study showed that isoenergetic meals high in carbohydrate or fat content induced a decrease in MAP within 60 min in elderly but not in younger persons, whereas HP meals did not reduce MAP (10). Differences in the postprandial release of the incretin hormone glucagon-like peptide 1 (GLP-1) may have contributed to the difference in postprandial BP between groups, because GLP-1 is known to affect BP (20) and GLP-1 release can be modulated by diet (21). Differences in plasma osmolality after consumption of the 2 supplements may also have affected the BP response (22). However, we did not measure GLP-1 and osmolality in our study.

Previous studies on postprandial BP responses have suggested that SBP is maintained or even increased after food consumption (18, 23–28). However, decreases in MAP, SBP, and/or DBP have also been reported (12, 13, 18, 23–25, 29–31). BP responses to a meal can vary depending on meal composition, meal size, and the individuals being studied. Studies comparing HP with HC meals did not report differences in postprandial BP responses between meals (9, 11–13). Three of these studies (9, 11, 12) measured postprandial BP only for 1–2 h and included a small number of participants (n ≤ 10), which may explain why no significant differences were found. The fourth study, by Pal and Ellis (13), measured postprandial BP for 6 h and included 20 women. In this study the high fat content (45% of energy) of the meals may have masked differences in postprandial BP between the HC and HP meals. Although the abovementioned studies, unlike ours, did not show a difference in postprandial BP responses between HC and HP meals, large postprandial decreases in BP after carbohydrate consumption have been described in persons with postprandial hypotension (32). After 4 wk of supplementation, the between-group differences in postprandial BP had disappeared because the postprandial decrease in BP in the HP group had become larger after 4 wk of supplementation, whereas the postprandial response after the carbohydrate-supplemented diet had not changed over 4 wk. Because other hemodynamic variables did not significantly change over 4 wk of supplementation, we cannot explain why the postprandial BP response declined in the HP group.

We expected lower postprandial SNS activity in the HP group, but this was not observed in the present study. Although postprandial NE was not significantly elevated, venous plasma NE concentrations showed postprandial patterns comparable to those reported by Penev et al. (33). No differences were found between our diet groups. Although plasma NE is an indicator of SNS activity, it only reflects whole-body sympathetic activation (34) and may be too insensitive to detect small differences in sympathetic activation on the whole-body level. In addition, it does not allow detection of regional differences in sympathetic activation (34), which are likely to be present (26). This is a clear limitation of our study. Another study looked at differences in muscle nerve sympathetic activity (MNSA) and found that the MNSA response was greater after glucose ingestion compared with after protein and fat ingestion. A mixed meal (44% carbohydrate, 36% fat, 20% protein) invoked an intermediate response, which did not differ from either the MNSA response to glucose or the responses to protein and fat (28). The tendency for a higher CO in the HC group after 4 wk (P = 0.08), although not reflected in higher HR and/or SV, could point to a higher level of sympathetic activation to the heart. Therefore, we cannot definitively exclude a differential level of sympathetic activation as a mechanism explaining the lower office BP and ambulatory BP in the HP group compared with the HC group in the overall PROGRES study (6).

This study has strengths and limitations. A strength of this study is that responses were measured during a whole day including 3 meals. Another strength is that the test days were conducted on d 1 and after 4 wk of supplementation to see whether differences between HP and HC meals would persist. A limitation of our study is that venous plasma catecholamines are not the most sensitive measure of SNS activity, but more direct measurements such as MNSA could not be implemented in our study protocol. Therefore, data on SNS activity after the HC and HP meals should be interpreted taking this limitation into account.

In conclusion, our data indicate that ingestion of an HP diet induces a smaller decrease in BP in overweight men and women with upper-range prehypertension or first-grade hypertension than ingestion of an HC diet on d 1. However, this difference was not present after 4 wk of treatment. The role of SNS activation in this adaptation needs further exploration using better techniques to measure (regional) sympathetic activation. These findings cannot explain the BP-lowering effect ascribed to dietary proteins.

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