Sympathetic Response to Oral Carbohydrate Administration

Evidence from Microelectrode Nerve Recordings

Christian Berne,* Jan Fagius,‡ and Frank Niklasson§
**Department of Internal Medicine,* ‡*Departments of Neurology and Clinical Neurophysiology, and* §*Department of Clinical Chemistry, University Hospital, Uppsala, Sweden*

Abstract

Microneurography was used to measure sympathetic outflow in human muscle nerves (MSA) for up to 90 min after the ingestion of 100 g D-glucose, 75.8 g D-xylose, intravenous D-glucose (0.35 g/kg), and 300 ml water. 19 healthy subjects were examined using a microelectrode positioned in the right peroneal nerve. MSA increased from 21±0.9 bursts/min at rest to 36.9±4.3 bursts/min 30 min after ingestion of D-glucose and from 18.9±2.9 to 26.3±3.4 bursts/min 30 min after D-xylose. The increase in MSA was already significant by 15 min. MSA had not returned to the basal level after 90 min. Neither intravenous D-glucose nor water intake enhanced MSA. MSA increased in parallel with plasma norepinephrine, and a significant correlation ($r = 0.55$; $P < 0.001$) was observed between the plasma insulin concentration and MSA after D-glucose ingestion. In three subjects the outflow of sympathetic nerve activity to the skin was examined after oral D-glucose and no change was observed, emphasizing the differentiated nature of the sympathetic nerve response to carbohydrate. Multiple factors such as insulin alone, hemodynamic adjustment to splanchnic vasodilation, and gastrointestinal distension are probably involved in the increased muscle nerve sympathetic outflow after carbohydrate ingestion.

Introduction

Carbohydrate feeding is accompanied by indices of increased activity in the sympathetic nervous system, both in experimental animals (1) and in human beings (2–4), whereas withdrawal of food causes an inhibition of sympathetic nerve activity, as assessed by measurements of norepinephrine turnover or plasma norepinephrine concentration (5–7). Nutrient intake also causes changes in cardiovascular hemodynamics. Increased heart rate and cardiac output were reported early (8) and have been confirmed in later studies. The precise cause of these cardiovascular changes is unknown, but an enhanced splanchnic blood flow with subsequent blood pressure alterations (9) may be important. On the other hand, the influence of nutrients on central sympathetic motoneurons (10) may contribute to the observed effects. Third, the finding of a dose-dependent increase in plasma norepinephrine after stepwise increase of plasma insulin, when blood glucose was clamped at a euglycemic level (11), leads to the suggestion that insulin alone is responsible for stimulation of the sympathetic nervous system.

So far, studies on the association between the intake of nutrients and sympathetic nervous system activity have relied on measurements of plasma norepinephrine (2–4, 6, 7), which represents the spillover from sympathetic nerve terminals (12), or on norepinephrine turnover in the rat heart (2, 5). It is well recognized that the sympathetic nervous system is a complex mixture of components, which usually are not activated together.

Microneurography permits exact mapping of the action of two subdivisions of the sympathetic nervous system (13). Muscle nerve sympathetic activity (MSA)[1] consists of vasoconstrictor signals governed by baroreflexes occurring in bursts strictly bound to the cardiac rhythm, and is involved in cardiovascular homeostasis. Skin nerve sympathetic activity (SSA) contains sudomotor and vasoconstrictor impulses, also appearing in bursts, but irregularly, without any overt connection to the heart rhythm, and is important for body thermoregulation (14).

In the present study we used microneurography to assess sympathetic nervous outflow under various conditions of carbohydrate intake. The sympathetic response was correlated with the changes in plasma glucose and serum insulin in healthy human beings.

Methods

Subjects. 27 microneurographic recordings were carried out after informed consent in 19 healthy nonobese volunteers (12 men and 7 women) aged 21–37 yr (mean 26.2 yr). The study was approved by the Human Ethics Committee of the Medical Faculty of the University of Uppsala.

Blood analyses. Plasma glucose was measured with a glucose oxidase technique using a glucose analyzer (model 2; Beckman Instruments, Inc., Palo Alto, CA).

Serum insulin RIA (PhadeSeph technique; Pharmacia Fine Chemicals, Uppsala, Sweden) and blood hematocrit (model S-plus Coulter counter; Coulter Electronics, Hialeah, FL) were measured by the routine service at the Department of Clinical Chemistry.

Blood for catecholamine analyses was collected in ice-chilled 10-ml Vacutainer tubes (Becton-Dickinson Co., Franklin Lakes, NJ) con-

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Address correspondence and reprint requests to Dr. Christian Berne, Department of Internal Medicine, University Hospital, S-751 85 Uppsala, Sweden.

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1. *Abbreviations used in this paper:* ANOVA, analysis of variance; MSA, muscle nerve sympathetic activity; SSA, skin nerve sympathetic activity.

taining 0.2 ml of a solution of EGTA (0.25 mol/liter) and glutathione (0.20 mol/liter). The plasma catecholamine concentration was measured with HPLC using electrochemical detection (15).

Nerve recordings. An insulated tungsten microelectrode (tip diameter ~ 5 μm) was inserted manually through the skin into the underlying right peroneal nerve below the fibular head, and a low impedance reference electrode was placed subcutaneously 2 cm away. The nerve was localized with the aid of electrical impulses through the recording electrode. When the nerve was encountered an electrode position within a muscle nerve fascicle was identified by the evoking of muscle twitches by electrical stimuli and the eliciting of afferent, mechanoreceptive activity by the stretching of the appropriate muscle. Corresponding criteria for a skin nerve fascicle position were the evoking of paresthesia without concomitant muscle twitch and the occurrence of mechanoreceptive afferent signals after gentle touch or pressure within the cutaneous receptive field of the nerve. Then minor adjustments of the electrode position were made until the characteristic pattern of multiunit MSA or SSA was observed. Briefly, the evidence that the signals recorded were of sympathetic origin was that (*a*) the activity was efferent, as shown by application of local anesthesia proximal and distal to the recording site; (*b*) the impulses were conducted with a velocity of ~ 1 m/s; (*c*) the activity was reversibly abolished by an intravenous infusion of the sympathetic ganglion blocking agent trimetaphan; and (*d*) changes of nerve activity correlate closely with sympathetic effector organ activity (14).

The nerve signal was amplified in two steps (total gain ×50,000) and fed through a 700–2,000-Hz band pass filter and an amplitude discriminator for improving signal/noise ratio. A resistance-capacitance integrating network (time constant 0.1 s) delivered a mean voltage display of the multiunit neural activity. During the experiments all recorded signals were displayed on a storage oscilloscope and the nerve signal was fed through a loudspeaker.

An electrocardiogram was recorded by chest electrodes and respiratory movements were monitored by a strain gauge strapped around the chest with a rubber band.

All recorded signals were stored on tape (FM tape recorder Sangamo Sabre VI; Sangamo Weston-Schlumberger, Sarasota, FL) for subsequent analysis.

General procedure. The experiments began at 8:00 a.m. and were carried out in a laboratory with an ambient temperature of 22–24°C. The subjects were fasting and had not smoked since midnight. After the insertion of an indwelling Teflon catheter (Venflon; Viggo, Helsingborg, Sweden) into an antecubital vein the subjects lay supine on a comfortable bed. Thereafter the nerve recording procedure was initiated. The search for a suitable recording position lasted from 10 to a maximum of 60 min. The sympathetic signals were then recorded throughout the experimental procedure. Before administration of the various carbohydrates or water the nerve activity was recorded at rest for 20 min. MSA was then recorded after oral administration of 100 g D-glucose in 300 ml water in seven subjects after an iso-osmolar load of 75.8 g D-xylose in 300 ml water in seven, and after intravenous D-glucose (0.35 g/kg body wt injected through a second indwelling catheter in the opposite arm) in seven. In three of the subjects to whom oral D-glucose had been given a second recording was carried out after ingestion of 300 ml water. One subject underwent all four procedures (c.f. Fig. 2). SSA was recorded after oral 100 g D-glucose in three subjects.

The oral or intravenous administration of carbohydrates or water took between 2 and 3 min and was carried out in the supine position. The subjects drank through a bent straw to minimize the risk of body movements (which can lead to displacement of the recording electrode). Blood samples for the analysis of plasma glucose, serum insulin, blood hematocrit, and plasma catecholamines were drawn at −15, 0, 15, 30, 45, 60, 75, and 90 min in relation to the oral intake, and at −15, 0, 4, 6, 10, 20, 30, 40, 50, 60, and 75 min in relation to the intravenous D-glucose.

Blood pressure was monitored noninvasively every third minute by an automated blood pressure recorder (EME 3200; EME Ltd., Brighton, UK).

The subjects were instructed to relax throughout the experimental procedure and to report any symptoms. They were questioned about the presence of symptoms every 15 min.

When SSA was recorded measures were taken to attain maximally relaxed conditions since SSA is markedly sensitive to emotional stress (16). Mental arithmetric (fast serial subtraction of two-figure numbers) was used as a stress test at regular intervals to induce short-lasting increases in SSA as a check of the recording position.

Analysis procedure. A 2.5 mm/s paper display of the neurogram and electrocardiogram on an ink-jet recorder (Siemens-Elema, Stockholm, Sweden) was used for determination of heart rate and the number of bursts of MSA per minute. These measurements were restricted to 6-min periods coinciding with the blood sampling occasions.

The total outflow of MSA/unit time can be defined as the product of the number and strength of the bursts (i.e., the number of impulses/burst, corresponding to the burst amplitude in the mean voltage neurogram). Since the recorded burst amplitude is critically dependent on the intraneural electrode position, it cannot be used for comparing the level of activity between individuals. However, during a given recording relative burst amplitude is representative of the level of activity (e.g., when the MSA response to a certain maneuver is compared with that during a control period), provided the electrode position remains unchanged. In five of seven experiments with oral D-glucose and six of seven with D-xylose this prerequisite was fulfilled and the mean burst strength for the period under analysis was taken as the mean of 50 consecutive bursts during a representative part of the period. A change of recording position was revealed by changes in signal/noise ratio, baseline level, and burst amplitude in the mean voltage neurogram; usually an experienced investigator can also easily detect the change in signal quality in the loudspeaker. Burst amplitude was measured in arbitrary units on a digitizing board (Hipad; Houston Instruments, Austin, TX) connected to a computer (Digital Dec 11/40; Digital Equipment Corp., Marlboro, MA).

Recordings of SSA were analyzed by inspection only, since a lack of change after oral glucose was clearly obvious (see Results, Fig. 3).

Statistics. Results are expressed as mean±SEM. The significance of changes in experimental variables was tested by analysis of variance (ANOVA) and *t* test for paired data. In all experiments the tests for significant changes over time were related to the basal value obtained immediately after the 15-min baseline period (0-min value). For the calculation of the correlation coefficient linear regression analysis with *t* test was used.

Results

No symptoms were reported during or after the experiments with D-glucose or water administration. In two subjects ingestion of D-xylose was followed by abdominal discomfort and diarrhea. These symptoms, however, did not occur until after the experiment was finished.

Sympathetic activity

The oral intake of 100 g D-glucose was followed within 15 min by an increase in MSA, peaking after 30 min and thereafter gradually returning toward basal levels, which, however, were not reached during the period of observation (Fig. 1). An equimolar load of D-xylose induced a similar but less intense increase ($P < 0.001$ for both; ANOVA). In contrast, neither intravenous glucose nor water elicited any significant increase of MSA, although there was a trend toward a gradual late increase.

Also, MSA burst amplitude increased in all subjects after the D-glucose and D-xylose loads, mean increases being 31 and 30%, respectively, from initial rest to the time of maximal outflow.

Representative samples from the mean voltage neurograms obtained in one individual who was examined under all four experimental conditions are shown in Fig. 2.

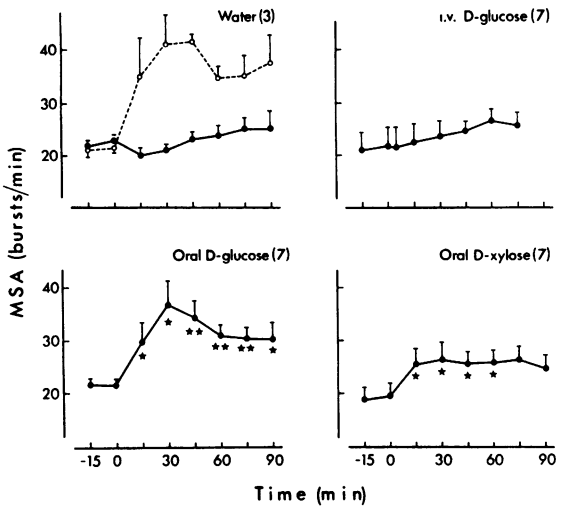

Figure 1. MSA, expressed as number of bursts per minute, after the administration of 100 g oral D-glucose, 75.8 g oral D-xylose, 300 ml water, and intravenous D-glucose (0.35 g/kg body wt). The MSA response to D-glucose in the three subjects who received water is included in the top left graph (○) Levels of significance with paired *t* test: $*P < 0.05$, $**P < 0.01$.

SSA was recorded in three subjects after oral D-glucose. All three subjects exhibited a low level of spontaneously occurring SSA throughout the experiment as shown in Fig. 3.

Catecholamines

The changes in plasma norepinephrine followed those of MSA, with significant increases after D-glucose and D-xylose ($P < 0.001$ for D-glucose and $P < 0.05$ for D-xylose; ANOVA) and with minor or no changes after water and intravenous D-glucose (Fig. 4). Plasma epinephrine did not increase under any of the experimental conditions.

Plasma glucose and serum insulin

Plasma glucose increased in the expected fashion after the 100-g oral glucose load, reflecting a normal glucose tolerance in all subjects (Fig. 5). After intravenous D-glucose the plasma glucose concentration reached its maximum after 4 min, followed by an exponential fall. The mean k value for the disappearance rate of glucose was 1.03%/min ($k = 100 \cdot {}^{e}\log 2/t_{1/2}$; $t_{1/2}$ = the time required to halve the glucose concentration as determined from the best fit of the measured values on semilogarithmic paper).

D-Xylose and water did not elicit any change in the plasma glucose concentration.

Oral or intravenous D-glucose resulted in an insulin response of the magnitude expected in a group of young healthy subjects (Fig. 5). D-Xylose caused a minor but significant increase of plasma insulin (from a fasting value of 7.1 mU/liter to a maximum at 15 min of 12.2 mU/liter), whereas no insulin response was observed after water.

There was a positive correlation ($r = 0.55$; $P < 0.001$) between MSA and insulin values in the experiments involving ingestions of D-glucose (Fig. 6). A weaker but significant correlation was also obtained after D-xylose ($r = 0.31$; $P = 0.02$).

Hematocrit

Hematocrit was monitored in all experiments since it represents an approximate measure of variations in plasma volume in situations when the erythrocyte mass can be considered constant (17).

The most profound changes in hematocrit were observed with intravenous D-glucose (Fig. 7) with a sharp early decrease reaching a nadir 4 min after termination of the glucose injection and lasting for ~ 20 min ($P < 0.001$; ANOVA).

Oral D-glucose caused only minor changes in hematocrit, whereas an increase was found with D-xylose ($P < 0.01$; ANOVA).

Hemodynamic changes

Blood pressure. Ingestion of D-glucose resulted in minor alterations of blood pressure (Fig. 8). In contrast, D-xylose ingestion resulted in significant increases in both systolic and diastolic pressures, which became evident 15 min after ingestion ($P < 0.001$; ANOVA).

Intravenous D-glucose tended to cause a decrease in blood pressure, whereas no blood pressure changes were noted in the three subjects given water.

Heart rate. Oral intake of D-glucose was associated with a minor but significant increase in heart rate ($P < 0.01$; ANOVA) (Fig. 9), whereas no such response was observed in the three subjects who received water. After D-xylose there was a tendency to a late increase in heart rate, which, however, did not attain statistical significance.

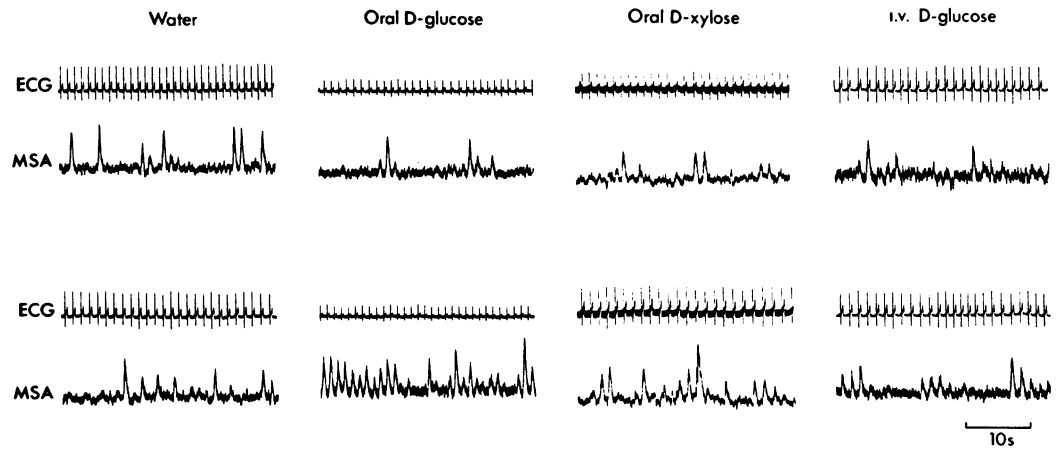

Figure 2. Mean voltage neurograms obtained in one subject who received 300 ml water, 100 g oral D-glucose (in 300 ml water), 75.8 g oral D-xylose, and intravenous D-glucose (0.35 g/kg body wt). Recordings of MSA at rest are depicted in the upper panel and MSA after the respective loads in the lower panel.

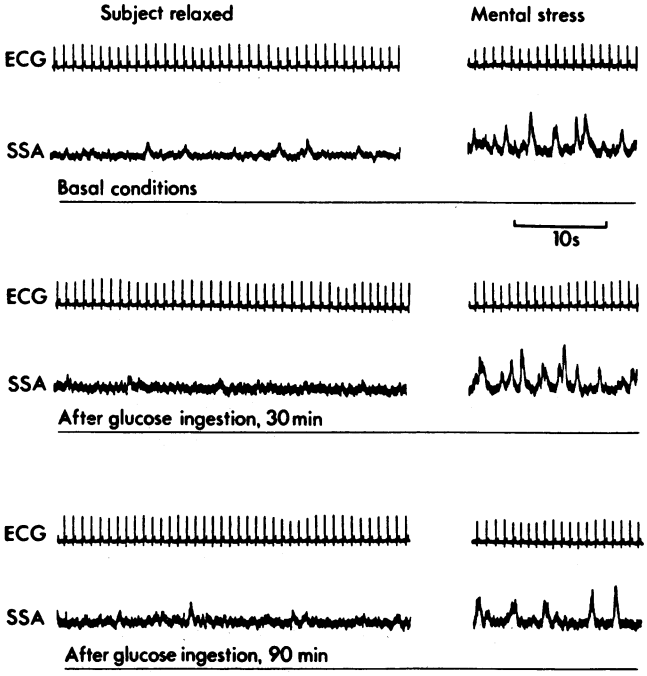

Figure 3. Representative examples from a recording of SSA in one subject after 100 g oral D-glucose. Examples from the recording at rest, as well as 30 and 90 min after D-glucose ingestion are shown. SSA after stress evoked by mental arithmetics is shown on the right.

No change in respiratory pattern was observed during any of the procedures.

Discussion

The principal finding of this study was that the oral intake of D-glucose and D-xylose was followed by an early and sustained increase of sympathetic outflow in peripheral nerves conducting impulses to limb muscle vasculature. The increase comprised both the number of bursts and the strength of individual bursts. It has been convincingly demonstrated that MSA represents the sympathetic outflow in vasoconstrictor fibers to the resistance vessels of skeletal muscle involved in cardiovascular homeostasis (14). In contrast, there was no response of the sympathetic nerve activity governing sweating or cutaneous vasoconstriction.

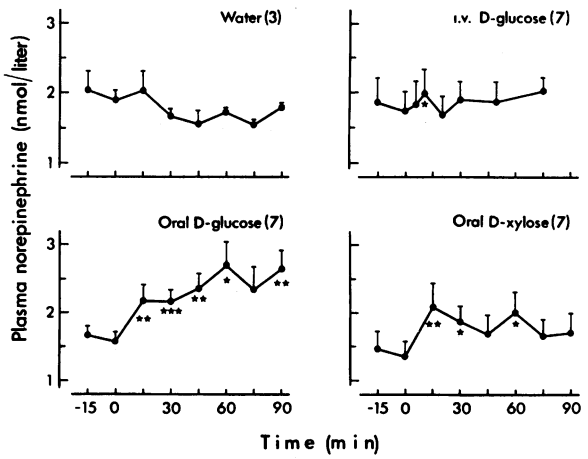

Figure 4. Venous plasma norepinephrine changes after the administration of 100 g oral D-glucose, 75.8 g oral D-xylose, 300 ml water, and intravenous D-glucose (0.35 g/kg body wt). $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

Previous studies of the sympatho-adrenal activity pattern after nutrient intake have relied on the measurement of plasma norepinephrine or catecholamine turnover. They have suggested that intake of carbohydrates, fats, proteins, and mixed meals acts as a general stimulus to the sympathetic nervous system with the exception of the adrenal medulla, since epinephrine does not increase until after several hours (4, 18). Microneurography enables us to analyze separately the responses of MSA and two modalities of the skin nerve sympathetic activity (SSA), namely, cutaneous vasoconstriction and sudomotor function, and the present study clearly demonstrates that oral carbohydrate intake is a stimulus only for MSA, whereas the other two functions under study remained uninfluenced. These findings, together with the lack of epinephrine release, suggest that the responses of the other subdivisions of the sympathetic nervous system may also react in differentiated ways to a carbohydrate load.

The absence of SSA could indicate either true lack of sympathetic outflow or loss of the recording position. The latter possibility was excluded, since all three subjects responded throughout the experiments with an increase of SSA on performing mental arithmetic (Fig. 3).

MSA increased after oral intake of D-glucose and D-xylose but not after water and intravenous D-glucose. The last observation seems surprising in view of the increase after oral glucose, but since this difference is consistent with the norepinephrine changes after the two types of D-glucose administration, the lack of MSA response to intravenous D-glucose is regarded as a true observation and not an experimental artifact.

One cannot draw any definite conclusions from the tendency to a late increase in MSA observed after water and intravenous D-glucose since experience from a long series of long-term microneurographic recordings with subjects in the supine position suggests that the experimental conditions (which require a minimum of bodily movements) will in some subjects lead to a feeling of discomfort after a couple of hours. We therefore cannot exclude that this may have contributed to the minute late increase in sympathetic nervous outflow (19).

MSA has been shown to correlate with venous plasma norepinephrine at rest (20, 21) and during certain maneuvers that change the outflow (22–25). It has been suggested that spillover from sympathetic nerve terminals in the vasculature of skeletal muscles underlies this relationship (20). The parallelism between the MSA and norepinephrine responses to glucose and xylose intake suggests that we have identified one important origin of the increase in plasma norepinephrine that has been reported after oral D-glucose (2–4, 18).

In both primates (9) and dogs (26) ingestion of food leads to an increase in splanchnic blood flow, a decrease in skeletal muscle blood flow, and an increase in cardiac output. Since MSA is mainly involved in stabilizing blood pressure at a given level (27, 28) the increase in MSA may play a functional role in this redistribution of blood, possibly as a baroreflex-induced counteraction of the tendency to a fall in systemic blood pressure secondary to the splanchnic vasodilation. No fall in blood pressure was detected in the present study. Due to the inter-

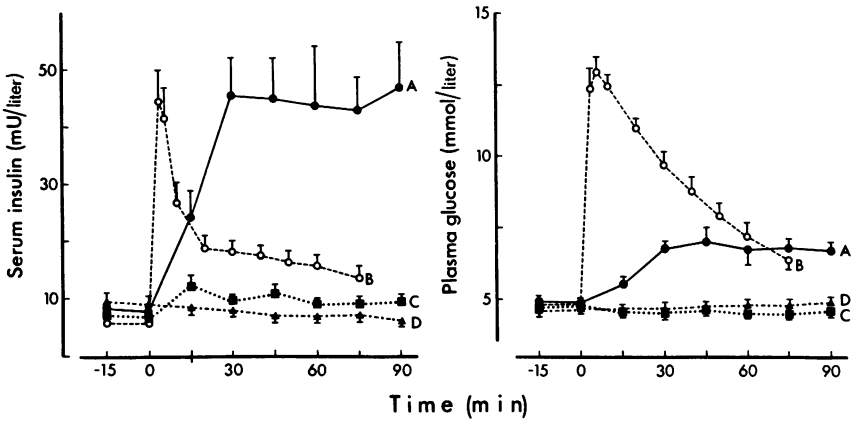

Figure 5. Serum insulin and plasma glucose concentrations after the administration of 100 g oral D-glucose (*A*), intravenous D-glucose (0.35 g/kg body wt; *B*), 75.8 g oral D-xylose (*C*), and 300 ml water (*D*).

mittent nature of our blood pressure recordings minor fluctuations in blood pressure may have escaped detection, however (c.f. Fig. 8). Therefore, we cannot completely exclude the possibility that the increase of MSA after oral D-glucose was precipitated by a tendency to blood pressure reduction, which has been reported to be severe in patients with disturbances of autonomic function (29). If not baroreflex-induced, the increase in MSA might be due to other mechanisms not elucidated by the present study, such as direct effects on central sympathetic motoneurons or possibly centripetal impulses from dilating splanchnic vessels (30). Since water ingestion induced no change of MSA, afferent activity from mere gastrointestinal distension (31) is not believed to underlie the observed effect; on the other hand, influences from gastrointestinal glucoreceptors (31) cannot be excluded.

MSA also responds to unloading of intrathoracic volume receptors at constant blood pressure (32), thereby indicating that it has a role in the adjustments to plasma volume changes. Oral D-xylose was accompanied by a 4% increase in hematocrit, indicating hemoconcentration, which persisted throughout the experiment and was not seen with the other loads. The corresponding fall in plasma volume can be approximated to 150 ml (17). Thus a plasma volume contraction after osmotically induced water loss to the bowel may have contributed to the increase of MSA after D-xylose ingestion by unloading plasma volume receptors.

The D-xylose load was also followed by an increase in blood pressure, coinciding with the enhanced level of MSA. This coincidence cannot be explained by baroreflex action (c.f. above) since MSA should be inhibited by an increase in blood pressure (22, 27, 28). A separate input to central sympathetic neurons (e.g., from the splanchnic vasculature) changing the baroreflex-inhibiting level could be reconciled with a blood pressure increase as a consequence of sustained increase in sympathetic outflow to muscle resistance vessels. This would resemble the mechanisms operating under other experimental conditions, such as isometric muscle contraction (24), the cold pressor test (33), and simulated diving (34), in which an increase in MSA is associated with an elevated blood pressure.

Role of insulin. Injection of insulin in insulin-dependent diabetic patients with autonomic failure can lead to hypotension (35) even in the absence of hypoglycemia. It has been suggested that normally this hypotensive action of insulin is balanced by a sympathetic nerve response leading to vasoconstriction.

In the present study there was a close parallelism between serum insulin levels and MSA after oral D-glucose (Fig. 6), an observation that may suggest that the increase of insulin is partly the cause of the increase in MSA. If so, the lack of MSA response during the short-lasting increase in serum insulin after intravenous D-glucose is unexpected at first sight. However, the incongruence might be explained by a simultaneous inhibition by volume receptor stimulation. The rapid drop in hematocrit after the injection of 100 ml D-glucose (Fig. 7) can

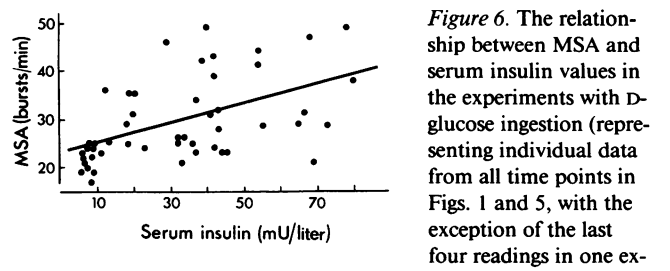

Figure 6. The relationship between MSA and serum insulin values in the experiments with D-glucose ingestion (representing individual data from all time points in Figs. 1 and 5, with the exception of the last four readings in one experiment in which the insulin measurements were lost due to technical failure). $r = 0.55$; $P < 0.001$.

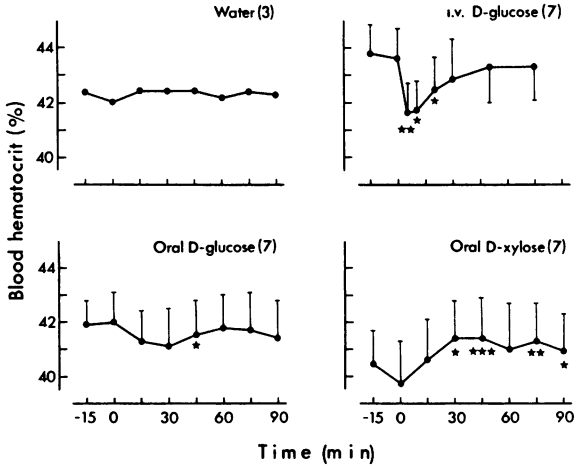

Figure 7. The changes in blood hematocrit after the administration of 100 g oral D-glucose, 75.8 g oral D-xylose, 300 ml water, and intravenous D-glucose (0.35 g/kg body wt). $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

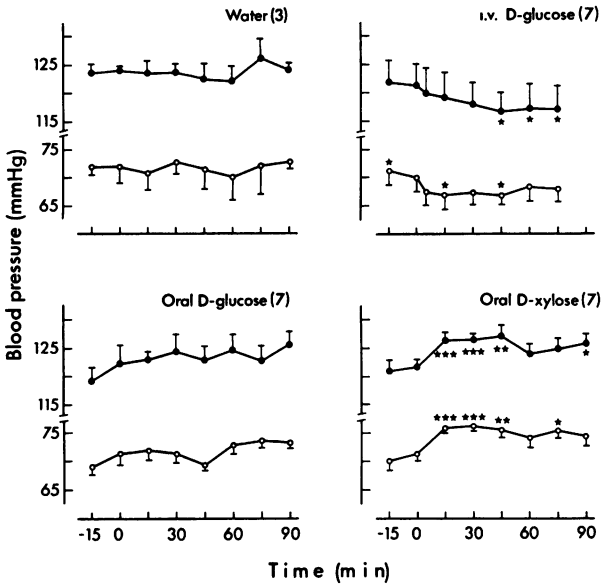

Figure 8. Blood pressure changes after the administration of 100 g oral D-glucose, 75.8 g oral D-xylose, 300 ml water, and intravenous D-glucose (0.35 g/kg body wt). $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

be calculated (17) to represent an expansion of the plasma volume by ~ 210 ml (probably caused by a combination of the 100-ml injection of the D-glucose solution and the osmotically mediated movement of water from extravascular to intravascular spaces). Since blood transfusion induces a reduction of MSA (Wallin, G., personal communication) the plasma volume expansion may be sufficient to prevent a stimulating effect of intravenous D-glucose on MSA. Observations with the euglycemic insulin clamp have indicated that more prolonged hyperinsulinemia can stimulate the sympathetic nervous system (11).

It is unlikely, however, that the small increment of insulin (from 7.1 to 12.2 mU/liter) after D-xylose is the sole determinant of the increase in MSA. D-Xylose, which was given in a load iso-osmolar with D-glucose in the present study, has previously been found to induce a long-lasting increment of plasma norepinephrine (18). The mere ingestion of carbohydrate (but not water only), with its hemodynamic consequences as indicated above, may also contribute to the xylose-induced effect. Thus the MSA response to oral D-glucose and D-xylose, although similar at first sight and induced by related chemical compounds, may well represent quite different underlying mechanisms.

Clinical implications. In elderly patients or in subjects with autonomic dysfunction or after sympathectomy (29, 36, 37) food intake is accompanied by blood pressure reductions, which may sometimes lead to syncope. The observed increase in MSA probably represents a neurally-mediated counteraction or prevention of any tendency to a fall in blood pressure, a lack of which would have pathophysiological consequences.

The increase in sympathetic nerve activity after feeding may also be viewed from the wider perspective of blood pressure regulation, overfeeding, and obesity. When obese subjects were subjected to caloric restriction there were parallel decreases in basal insulin, norepinephrine, and blood pressure (7, 38). This observation, as well as epidemiological data demonstrating a close association between obesity, hyperinsulinemia, and hypertension (39), form the basis for a hypothesis linking these three factors in the pathogenesis of essential hypertension, particularly in obese people (40). If insulin is an important stimulus for the increase in MSA after carbohydrate intake, insulin resistance with prolonged hyperinsulinemia might provoke repeated and sustained nerve commands to vasoconstriction in the vascular beds of major importance for blood pressure regulation, eventually leading to hypertension.

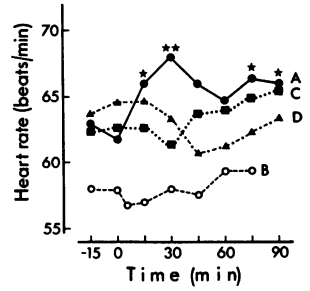

Figure 9. The changes in heart rate during the experiments with 100 g oral D-glucose (*A*), intravenous D-glucose (0.35 g/kg body wt; *B*), 75.8 g oral D-xylose (*C*), and 300 ml water (*D*). $*P < 0.05$, $**P < 0.01$.

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