Effects of Intravenous Fructose Infusion on Sodium Handling and Peripheral Vascular Tone in Pre-Hypertensive Subjects

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The hemodynamic and humoral effects of i.v. fructose infusion and a control infusion were studied in 12 borderline hypertensive patients according to a single-blind, cross-over, randomized protocol. Fructose infusion decreased urinary sodium excretion and significantly increased plasma insulin, plasma Na^+/K^+ ATPase inhibitory activity, and forearm arterial and venous tone (+13%), the last of which was not observed during the control infusion (-2.5%). Levels of ANF and PRA in plasma were not altered by either infusion. We conclude that the sodium retention caused by acute i.v. fructose loading could be related to the increase in plasma insulin levels, which may directly affect individual susceptibility to sodium by enhancing sodium reabsorption at renal tubules. This sodium retention could contribute to the release of a plasma Na^+ -pump inhibitor apparently unrelated to extracellular volume expansion and potentially responsible for the early peripheral vascular involvement found in hypertension-prone men. (*Hypertens Res* 1994; 17: 239-242)

Key Words: fructose, sodium, borderline hypertension

Recent reports indicate that Sprague-Dawley rats on a fructose-enriched diet develop a progressive increase in arterial blood pressure apparently unrelated to changes in body weight or in the renin-angiotensin-aldosterone system (1, 2). The mechanisms responsible for this increase are still poorly understood, and the hyperinsulinemia that occurs when animals are fed a high-fructose diet may be involved (2, 3). A role for insulin metabolism in the pathogenesis of arterial hypertension has been repeatedly suggested, and hyperinsulinemia and insulin resistance have been reported in experimental (1) and human hypertension (4). In particular, by reduction of urinary sodium excretion (5, 6) insulin could contribute to the development of sodium-dependent hypertension via promotion of extracellular volume expansion or interference with the neuro-humoral pathway, or both (1). More recently, plasma insulin levels were found to directly affect the salt-dependent increase in blood pressure in Dahl rats (7). To further clarify this latter issue, we studied the effects of fructose infusion on some humoral mechanisms thought to be involved in the development of salt-related hypertension (8). In particular, the present study was done to investigate the relationship between fructose loading, sodium balance, and insulin release in young patients with borderline hypertension.

Materials and Methods

The subjects were 12 young (age 24 ± 4 years) borderline hypertensive patients (9 men and 3 women) with normal plasma renin activity. Secondary hypertension was excluded by physical and laboratory examination. All the patients were free of anti-hypertensive medications and all kept to a constant daily sodium intake of 100 mmol for 7 days before the study. Patients were studied in a metabolic ward at a constant room temperature of 24°C and after 30 minutes of rest in a recumbent position. The responses to a 2-hour i.v. infusion of high-dose isotonic fructose (0.25 ml/min/kg b.w. FRUCT) and low-dose isotonic fructose (0.025 ml/min/kg b.w. CONTROL) were measured in a single-blind, randomized, crossover study. During the study the carbohydrate and sodium intake were kept unchanged and the two tests were done 48 hours apart. The study protocol was approved by the Ethical Committee of the University of Bologna and informed consent was obtained from each patient before inclusion in the trial. Heart rate, and systolic, diastolic, and mean blood pressures were measured with an automatic device (Sentry Automated Screening Devices, Costa Mesa, CA) and the values reported are means of five consecutive measurements. Fore-

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arm blood flow (FBF), vascular resistance (FVR) and venous distensibility were determined by venous occlusion plethysmography with a single-strand mercury-in-silastic strain gauge, according to a standard method (9, 10). The venous volume at a congesting pressure of 30 mmHg above the minimum occlusion pressure was derived for each subject and expressed as VV_{30} . Plasma renin activity (PRA), plasma aldosterone, and plasma insulin were measured by radioimmunoassay. Plasma and urinary sodium and potassium were measured by flame photometry. Levels of atrial natriuretic factor (ANF) in plasma were determined by commercial radioimmunoassay (Amersham ANP R.I.A. System, Amersham Radiochemical, Buckinghamshire, U.K.) after plasma purification on Bond-Elut C-18 disposable columns (Analytichem International, Harbor City, CA). Levels of an endogenous inhibitor of Na^+/K^+ ATPase, whose biochemical characteristics have been previously published (11), were measured in plasma by enzyme-coupled assay as described elsewhere in detail (9, 10). To exclude the interference of a fructose-induced rise in plasma lipid concentration on the increase in Na^+/K^+ ATPase inhibitory activity (12), 10 boiled plasma extracts with high levels of Na^+ -pump inhibitor were assayed before and after extraction with a hexane and hexane/ CHCl_3 (50/50), mixture to remove lipids from the samples, and the results were compared.

The protocol was as follows. Immediately before infusion, a baseline blood sample was obtained from an antecubital vein. Then baseline blood pressure and forearm hemodynamics were determined. The measurements were repeated and blood was sampled again after 120 min of fructose infusion. The rates of urinary excretion of sodium and potassium during the 24 h after fructose loading were calculated both cumulatively (0 to 24 h) and in two separate specimens defined as immediate (0 to 2 h) and delayed (2 to 24 h). Results are expressed as mean $\pm$ SD. Two-way analysis of variance for cross-over-

design experiments was used to compare the effects of fructose loading on normally distributed variables. In the presence of significant values of " f ", the Least Significant Difference test was applied and p values > 0.05 were rejected. The paired Student's " t " test was used to compare baseline characteristics of patients.

Results

Cumulative urinary sodium excretion was significantly lower during FRUCT loading than during CONTROL (2.22 ± 0.8 vs. 2.82 ± 0.6 $\mu\text{mol}/\text{min}/\text{kg}$; $p < 0.05$) and the difference resulted mainly from a lesser immediate natriuresis (0.30 ± 0.07 vs. 0.45 ± 0.1 $\mu\text{mol}/\text{min}/\text{kg}$; $p < 0.05$). Delayed sodium excretion was also lower, but the difference was not statistically significant (1.92 ± 0.5 vs. 2.4 ± 0.8 $\mu\text{mol}/\text{min}/\text{kg}$; N.S.) because of the small sample size. The effects of two-hour FRUCT and CONTROL infusions on the hormonal and hemodynamic variables are summarized in Table 1. Fructose infusion caused a significant increase in plasma levels of endogenous Na^+/K^+ ATPase inhibitor. Such an increase was detected in 10 of the 12 patients. The increase was apparently independent of changes in plasma lipid concentration, since it was not prevented, and was even magnified by extraction of plasma lipids from the 10 samples showing a rise in Na^+/K^+ ATPase inhibitor (non-extracted 53 ± 19 vs. extracted 63 ± 17 ; $p < 0.005$). Conversely, levels of ANF in plasma were unchanged after both FRUCT and CONTROL infusions as were PRA, plasma aldosterone, and hematocrit. As expected, plasma insulin increased only after FRUCT and no significant relationships were found between changes in insulin and the hemodynamic and humoral responses to fructose challenge. Arterial blood pressure was unaffected by either infusion, but a mean increase in FVR and a decrease in VV_{30} was observed after FRUCT only. These occurred in 8 of the 10 patients in whom plasma

Table 1. Effects of Fructose and Control Infusions on Hemodynamic and Humoral Variables in Borderline Hypertensive Patients

	Baseline	Control	Baseline	Fructose
Systolic BP (mmHg)	131.5 ± 8	128.3 ± 10	132.5 ± 9	134.5 ± 7
Diastolic BP (mmHg)	75.4 ± 7	73.9 ± 7	75.0 ± 6	72.2 ± 5
Heart rate (b/min)	68.4 ± 7	64.9 ± 6	68.2 ± 7	62.4 ± 7
FBF (ml/min/100 ml)	3.7 ± 1	3.6 ± 1	3.6 ± 1	3.1 ± 0.9
FVR (units)	28.9 ± 5	28.0 ± 5	28.3 ± 5	$33.3 \pm 4^{**}$
VV_{30} (ml/100 ml)	1.7 ± 0.3	1.7 ± 0.3	1.7 ± 0.3	$1.5 \pm 0.3^*$
PRA (ng/ml/h)	1.8 ± 1	1.6 ± 1	1.8 ± 1	1.4 ± 1
Pl. Aldosterone (pg/ml)	261.0 ± 67	162.0 ± 56	223.0 ± 80	140.0 ± 86
ANF (pg/ml)	22.9 ± 9	23.1 ± 8	23.4 ± 8	24.7 ± 9
Na^+/K^+ ATPase inhibition (%)	37.5 ± 8	35.1 ± 9	35.0 ± 1	$47.5 \pm 11^{**}$
Plasma glucose (mg/dl)	85.3 ± 11	81.2 ± 9	87.4 ± 8	$108.6 \pm 20^{**}$
Plasma insulin (U/ml)	12.1 ± 3	11.6 ± 5	11.4 ± 3	$17.6 \pm 6^{**}$
Hematocrit (%)	45.4 ± 3	45.1 ± 3	45.1 ± 3	44.0 ± 2

*, ** $p < 0.05$, $p < 0.05$ compared to first baseline value.

Na^+/K^+ ATPase inhibitory activity increased in response to the infusion.

Discussion

The present study shows that i.v. fructose infusion has an antinatriuretic effect in borderline hypertensive patients. This effect seems to be related to an increase in plasma insulin levels, whose ability to promote sodium reabsorption has been recently confirmed in salt-sensitive animals with sodium retention and an increase in blood pressure during insulin infusion. These data suggest that plasma insulin, sodium, and high blood pressure are directly related (7). Since human borderline hypertension has been classified among the salt-related conditions (13), the present data largely support the experimental observations on insulin and sodium handling and suggest that plasma insulin is very much involved in the activation of mechanisms that contribute to the development of salt-related hypertension. Despite the sodium retention, we found no concomitant increase in blood pressure in response to fructose infusion. Since a pressor increase after fructose overload has been reported in animals on a fructose-enriched diet (1, 2), we believe that the *acute* nature of the i.v. fructose loading in the present study did not allow for a sustained hyperinsulinemia or for an adequate change in extracellular volume, or both. Indeed, the hypertensive effects of insulin have been observed only in response to continuous insulin infusion (7) or, as in the study by Hwang *et al.* (2), in a setting where high oral fructose was associated with indirect evidence of extracellular volume overload (suppression of the renin-angiotensin-aldosterone system and an increase in ANF). In the present study, the occurrence of sodium retention and forearm vasoconstriction without pressor changes suggests that insulin may increase blood pressure through an initial sodium-vasoconstriction pathway. The pathophysiological factor linking such a pathway to high blood pressure could be the plasma Na^+/K^+ ATPase inhibitor. The levels of this inhibitor increased significantly during fructose loading despite the lack of volume expansion, which suggests that such a humoral factor is relatively independent of changes in circulating volume distribution. This observation is in agreement with the data of Hamlyn *et al.* (14) who reported a sudden increase in plasma levels of Na/K ATPase inhibitor not associated with changes in plasma volume during the early antinatriuretic phase of DOCA-salt hypertension. However, since most studies have related the release of a Na/K ATPase inhibitor to extracellular volume expansion (8) we would like to provide some tentative explanations for the release of a Na/K ATPase inhibitor without changes in plasma volume. First, some degree of volume expansion may have occurred early in the fructose infusion when we did not measure any index of plasma overloading. Alternatively, the degree of volume expansion achieved in response to fructose infusion (reduction of hematocrit from 45.1% to 44.0%) even if not statistically significant,

may have been sufficient to cause the release of a Na/K ATPase inhibitor. Finally, plasma insulin *per se* or the increase in sympathetic activity that follows hyperinsulinemia (15) may have been sufficient to stimulate the release of an endogenous Na/K ATPase inhibitor. Indeed, an increase in the level of Na/K ATPase inhibitor, and an increase in inhibitory activity have been reported in some settings not associated with volume expansion, such as water depletion (16), elevation of intracerebral sodium levels (17), and intracisternal administration of the dopamine-receptor agonist pergolide (18).

The increase in the level of the Na^+ -pump inhibitor in plasma is specific in nature: the extraction of samples with hexane to remove the lipids and prevent their interference in the enzyme-coupled assay increased the degree of Na^+/K^+ ATPase inhibition. The vasoconstrictive properties attributed to Na^+/K^+ ATPase inhibitors (8) could explain the increase in forearm vascular resistance and venous tone observed in the present study during fructose infusion. The vasoconstrictive effects of Na/K ATPase inhibition seem to be stronger than the reported vasodilating activity of hyperinsulinemia (19), which is critically dependent on the indirect activation of Na/K ATPase in the vessel wall (20). We speculate that the brisk reduction in sodium excretion observed during acute fructose infusion promoted the release into the bloodstream of Na^+/K^+ ATPase inhibitor to counteract sodium retention by mechanisms that do not necessarily cause an immediate natriuretic response (8). A similar prompt increase in endogenous Na^+/K^+ ATPase inhibitor occurring without a significant increase in blood pressure and a with fall in plasma levels of ANF has been reported to occur during the early antinatriuretic phase of DOCA-induced hypertension (14). Interestingly, the lack of ANF response reported by Hamlyn (14) and confirmed by our results in a different setting (21), could contribute to the rise in plasma Na^+ -pump inhibitor by precluding the described inhibitory influence of stimulated ANF on the secretion of such plasma factors (14, 21, 22).

In conclusion, our present data support the hypothesis that the increase in plasma levels of insulin that follows intravenous fructose infusion promotes renal sodium reabsorption and peripheral vasoconstriction, and thereby contributes to the development of salt-sensitive hypertension. We also suggest that insulin may act through a sodium-vasoconstriction pathway modulated by an endogenous Na^+ -pump inhibitor, which is released into the bloodstream when renal sodium reabsorption is high, and is responsible for the early peripheral vascular abnormalities found in borderline hypertensive patients before the development of stable hypertension.

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