Role of the Kidney in the Metabolism of Fructose in 60-hour Fasted Humans

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SUMMARY

Arterial (A) and renal venous (RV) concentrations and net splanchnic exchange of glucose, fructose, lactate, pyruvate, glycerol, and alanine were studied in the basal state and during a 135-min intravenous infusion of fructose at 2 mmol/min in healthy subjects after a 60-h fast. After 45 min of the fructose infusion, somatostatin (9 μg/min) was infused for 60 min to induce hypoglucagonemia.

Fructose infusion resulted in a net uptake of this hexose by the kidney as well as the splanchnic bed. Estimated renal uptake of fructose could account for the disposal of 20% of the administered fructose load while splanchnic uptake accounted for 38%. The fructose infusion resulted in a rise in blood glucose of 0.9 mmol/L, a 35% increase in net glucose output from the splanchnic bed, and a consistent net output of glucose from the kidney (A-RV = -0.17 ± 0.05 mmol/L as compared with 0 ± 0.03 in the basal state, $P < 0.02$). Net glucose release from the kidney could account for 55% of the net renal uptake of fructose. The fructose infusion also resulted in a marked change in renal lactate balance from a net uptake in the basal state ($A - RV = 0.05 \pm 0.01$ mmol/L) to a net output during fructose administration ($A - RV = -0.10 \pm 0.04$). Administration of somatostatin resulted in a fall in arterial glucagon levels and a 35% decrease in splanchnic glucose output but failed to alter the arterial-renal venous difference for glucose observed during the fructose infusion.

We conclude that in 60-h fasted man: (a) intravenous infusion of fructose results in a net uptake of this hexose by the kidney as well as the liver, (b) this uptake is accompanied by stimulation of renal as well as hepatic glucose production and renal production of lactate, and (c) hypoglucagonemia inhibits splanchnic but not renal glucose output during fructose infusion.

These data indicate that the kidney is an important site of fructose disposal and that glucose and lactate are end products of renal fructose metabolism.

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The liver is well recognized as an important site of fructose metabolism in man.[1] Following the intravenous administration of fructose a consistent uptake of fructose by the splanchnic bed[2–4] and an increase in liver glycogen[4,5] are observed. Despite these data on hepatic fructose metabolism, the effect of intravenous fructose administration on splanchnic glucose balance is not established. Increased splanchnic glucose release,[2] inhibition of splanchnic glucose release,[4] and inconsistent effects on net splanchnic glucose exchange[3] have been reported. These differences may in part be related to differences in the doses of fructose employed, which have varied from 2 to 17 mmol/min.[2–4] It is noteworthy in this regard that when large doses of fructose (6–17 mmol/min) have been infused, a rise in blood glucose concentration of 60 mg/dl and an increase in muscle glycogen content are observed despite a reduction or complete inhibition of splanchnic glucose output.[4] The latter findings have been interpreted as indicating a direct uptake and conversion of fructose to glycogen in muscle and a diminution in muscle glucose uptake.[4] An alternative possibility, however, is that fructose infusion results in an increase in glucose production by an extrahepatic site. With respect to the latter possibility, the kidney is known to possess the enzymes necessary for conversion of fructose to glucose.[6] Furthermore, in a previous study involving a single healthy subject, Bergstrom and Hultman observed a net output of glucose from the kidney during the infusion of fructose at a rate of 1.3 g/min.[4] The role of the kidney in fructose metabolism is of particular interest in view of recent observations from our laboratory that individual glucose precursors (alanine and glycerol) differ in their ability to stimulate hepatic as opposed to renal gluconeogenesis.[7]

The present study was consequently undertaken to evalu-

ate further the role of the kidney in the metabolism of fructose and the effects of fructose infusion on net glucose release by the splanchnic bed and the kidney in 60-h fasted, glycogen-depleted humans. In addition, since our earlier studies have shown that hypoglucagonemia interferes with basal and alanine-stimulated glucose output by the splanchnic bed but fails to alter basal or glycerol-stimulated glucose production by the kidney,[7] we also examined the effects of somatostatin infusion on the splanchnic and renal responses to fructose infusion.

METHODS

Subjects. The subjects were 12 nonobese healthy male volunteers, 20–39 yr. Their body weight (mean 73 kg, range 53–93 kg) was within 10% of the ideal body weight (Metropolitan Life Insurance Tables). They were all informed of the nature, purpose, and possible risks involved in the study before giving their voluntary consent to participate. The procedures used were reviewed and approved by the institutional ethical committees.

Procedure. All subjects were studied in the morning after a 60–64-h fast. Two types of studies were performed: one involving renal vein catheterization (renal study) (N = 6), and the other using the hepatic vein catheter technique (hepatic study) (N = 6).

Renal study. Catheters were inserted percutaneously into a brachial artery, a renal vein, and a peripheral vein. The peripheral vein was to be used for fructose infusion. The renal vein catheter was guided to its position using fluoroscopic control. The subjects were studied before and during i.v. administration of fructose (2 mmol/min) for 135 min. After 45 min of fructose administration, somatostatin (generously supplied by Wyeth Laboratories, Radnor, Pennsylvania) was infused at a rate of 9 μg/min for 60 min. The fructose infusion was continued for 30 min after cessation of the somatostatin infusion.

Hepatic study. Catheters were inserted percutaneously into a brachial artery and a right-sided hepatic vein. The hepatic vein catheter was inserted via a femoral vein and advanced to its position under fluoroscopic control. A catheter to be used for infusions was also inserted in the femoral vein and positioned in the inferior vena cava. The experimental protocol regarding infusion of fructose and somatostatin was the same as in the renal study.

Hepatic blood flow was estimated with the constant infusion technique[8] using indocyanine green dye.[9]

Analytic methods. Blood samples for determination of substrates and hormones were obtained from the arterial catheter and the hepatic or renal venous catheters at timed intervals during the experiments.

Glucose was analyzed in whole blood by the glucose-oxidase reaction.[10] Lactate,[11] pyruvate,[12] glycerol,[13] alanine,[14] and fructose[15] were all determined enzymatically in whole blood. Plasma glucagon[16] and insulin[17] were determined by radioimmunoassay.

Data in the text, tables, and figures are given as mean ± SE. Standard statistical methods[18] were used and the paired t-test was used when applicable.

RESULTS

Arterial concentrations (Table 1). The effect of the fructose infusion on arterial substrate and hormone concentrations was virtually identical in the renal and hepatic study. Consequently, the data have been combined (Table 1). The fructose infusion resulted in a rise in blood fructose to values of 1.5–1.7 mM, as well as a 0.9 mM rise in blood glucose. As expected,[2,4] there was a rise in blood lactate, as well as increments in pyruvate and alanine. The fructose infusion also resulted in a 50% rise in plasma insulin and a 30% fall in plasma glucagon.

Following the addition of somatostatin, there were marked declines in plasma insulin and glucagon. The arterial glucose level showed a smaller rate of rise in the face of the somatostatin infusion as compared with fructose alone (0.008 mmol/L/min vs. 0.019 mmol/L/min). The somatostatin infusion also resulted in a threefold rise in blood glycerol. After cessation of the somatostatin infusion the arterial glucose level rose more rapidly. Plasma glycerol returned to basal levels.

Renal study (Table 2). In the basal state, no significant net renal exchange of glucose, pyruvate, or alanine was detected. A significant net renal uptake of lactate and glycerol was observed as judged from the arterial-renal venous differences ($P < 0.02$).

Administration of fructose resulted in a net uptake of fructose by the kidney ($P < 0.001$) as well as a significant net release of glucose by the kidney ($A - RV = -0.17 \pm 0.05$, $P < 0.02$). The net renal uptake of lactate observed in the

TABLE 1
Arterial concentrations of substrates and hormones in the basal state and during fructose infusion before, during, and after concomitant somatostatin administration in 60-h fasted humans

		Fructose infusion		
			Somatostatin infusion	
	Basal	45 min	105 min	135 min
Fructose (mmol/L)	—	1.58 ± 0.14‡	1.68 ± 0.15‡	1.47 ± 0.11‡
Glucose (mmol/L)	2.87 ± 0.09	3.73 ± 0.17‡	4.20 ± 0.37*	5.34 ± 0.44‡
Lactate (mmol/L)	0.56 ± 0.05	0.79 ± 0.05‡	1.02 ± 0.08‡	1.05 ± 0.11‡
Pyruvate (μmol/L)	44 ± 4	60 ± 8*	81 ± 6‡	81 ± 11‡
Alanine (μmol/L)	173 ± 13	181 ± 15	221 ± 18*	222 ± 21*
Glycerol (μmol/L)	71 ± 7	86 ± 10	202 ± 17‡	95 ± 20
Insulin (μU/ml)	10 ± 2	15 ± 2‡	6 ± 1*	24 ± 6*
Glucagon (pg/ml)	137 ± 28	88 ± 15*	52 ± 10†	102 ± 28

Significantly different from basal * $P < 0.05$, † $P < 0.01$, and ‡ $P < 0.005$.

TABLE 2
Arterial-renal venous difference of substrates in the basal state and during fructose infusion during and after concomitant somatostatin administration in 60-h fasted humans

		Fructose infusion		
			Somatostatin infusion	
	Basal	45 min	105 min§	135 min
Fructose (mmol/L)	—	0.30 ± 0.05‡	0.29 ± 0.05‡	0.16 ± 0.05‡
Glucose (mmol/L)	0 ± 0.03	−0.17 ± 0.05*	−0.18 ± 0.04†	−0.12 ± 0.07
Lactate (mmol/L)	0.05 ± 0.01	−0.10 ± 0.04*	−0.17 ± 0.05†	−0.15 ± 0.05†
Pyruvate (μmol/L)	4 ± 3	−15 ± 4‡	−5 ± 3	−4 ± 4
Alanine (μmol/L)	−2 ± 4	−16 ± 7	−18 ± 11	−20 ± 12
Glycerol (μmol/L)	17 ± 5	15 ± 11	45 ± 26	28 ± 13

Significantly different from basal * $P < 0.05$, † $P < 0.01$, and ‡ $P < 0.005$.
§ The values for glucose exchange obtained during the somatostatin infusion are the mean of four observations obtained at 15-min intervals after the start of the somatostatin infusion.

basal state changed to a net release ($P < 0.05$) when fructose was infused. A small net release of pyruvate and alanine also accompanied the infusion of fructose. The arterial-renal venous difference for glycerol was not significantly altered by the fructose infusion.

Addition of somatostatin to the fructose infusion failed to alter the arterial-renal venous differences for glucose, fructose, or lactate.

Hepatic study (Table 3). During the infusion of fructose, splanchnic glucose output (SGO) rose 35% above basal levels by 45 min. When somatostatin was added, SGO fell to basal levels. After cessation of the somatostatin infusion, SGO again rose, reaching values 88% above the basal level.

Fructose infusion resulted in a net uptake of fructose by the splanchnic bed of 0.75 mmol/min. Splanchnic uptake of lactate rose 50% above basal levels during the fructose infusion. In contrast, uptake of pyruvate, alanine, and glycerol were not altered during the fructose infusion. Addition of somatostatin resulted in a rise in glycerol uptake ($P < 0.01$) but failed to alter significantly lactate or alanine exchange.

The estimated hepatic blood flow was not significantly changed by the fructose infusion but reached values 11% below basal during the somatostatin infusion.

DISCUSSION

In the present study the effect of fructose infusion on net exchange of glucose, fructose, and gluconeogenic precursors across the kidney and splanchnic bed has been examined in 60-h fasted subjects. As pointed out previously,[7] inasmuch as 60-h fasting is known to result in liver glycogen depletion[19] and inasmuch as renal glycogen content is low,[20] changes in net glucose release from the splanchnic bed or kidney in 60-h fasted subjects are likely to reflect alterations in gluconeogenesis rather than glycogenolysis. Although measurements of renal blood flow were not obtained in this study, our previous investigations have shown that renal blood flow in 60-h fasted humans (1.3 L/min) is comparable to that observed after an overnight fast and is not affected by the administration of gluconeogenic substrates such as glycerol and alanine or the infusion of somatostatin.[7]

The present data demonstrate that infusion of fructose at a rate of 2 mmol/min results in a net uptake of this hexose by the splanchnic bed and an increase in net splanchnic glu-

TABLE 3
Splanchnic exchange of substrates and estimated hepatic blood flow in the basal state and during fructose infusion before, during, and after concomitant somatostatin administration in 60-h fasted humans

		Fructose infusion		
			Somatostatin infusion	
	Basal	45 min	105 min§	135 min
Fructose (mmol/min)	—	0.75 ± 0.07‡	0.72 ± 0.07‡	0.78 ± 0.10‡
Glucose (mmol/min†)	−0.25 ± 0.01	−0.36 ± 0.05*	−0.21 ± 0.03	−0.47 ± 0.06*
Lactate (mmol/min)	0.30 ± 0.02	0.45 ± 0.05*	0.54 ± 0.04†	0.57 ± 0.04†
Pyruvate (μmol/min)	22 ± 2	27 ± 6	41 ± 5*	45 ± 7*
Alanine (μmol/min)	87 ± 9	97 ± 11	101 ± 17	115 ± 18
Glycerol (μmol/min)	71 ± 12	83 ± 13	170 ± 16‡	82 ± 15
Hepatic blood flow (L/min)	1.24 ± 0.08	1.18 ± 0.05	1.10 ± 0.05*	1.28 ± 0.10

Significantly different from basal * $P < 0.05$, † $P < 0.01$, and ‡ $P < 0.005$.
§ The values for glucose exchange during the somatostatin infusion are the mean of six observations obtained at 5–15-min intervals after the start of the somatostatin infusion.

cose output. Although previous studies have clearly shown that the liver is a major site of fructose uptake, the data have been conflicting regarding the effects of fructose administration on splanchnic glucose release.[2–4] These differences may be due, in part, to varying doses of fructose (2–17 mmol/min) that have been employed in those studies.[2–4] The decrease in splanchnic glucose output reported in a previous study[4] thus may be related to the three- to sixfold higher doses of fructose employed in that study as compared with the present investigation, and the accompanying greater rise in blood glucose (to 8 mM). A rise in blood glucose would be expected to have an inhibitory effect on splanchnic glucose release.[21] Furthermore, previous studies with glucose have shown that as one increases the rate of infusion from 2 to 25 mg/kg/min the effect on net splanchnic glucose balance changes from partial inhibition of output to a net uptake.[21] In addition to differences related to altered dose levels, the stimulatory effect of fructose on splanchnic glucose output observed in the present study may also be a reflection of the increase in activity of gluconeogenic enzymes which is known to occur in starvation.[22]

In addition to its effects on splanchnic metabolism, fructose infusion resulted in a consistent net uptake of this hexose by the kidney. Furthermore, the fructose infusion was accompanied by a consistently negative arterial-renal venous (A-RV) difference for glucose, indicating stimulation of renal glucose production. The relationship between the A-RV differences for glucose and fructose indicates that net renal glucose output could account for over 50% of renal fructose uptake. These observations thus indicate that the kidney is a site of fructose disposal in man and that conversion to glucose is an important fate of the fructose taken up by the kidney.

The current findings are consistent with a previous report that the kidney is a locus of fructose metabolism and that fructose stimulates renal glucose release in the rat.[23] In addition, in an earlier study in a single human subject, fructose infusion resulted in a net output of glucose from the kidney.[4] The renal gluconeogenic effect of fructose may also provide an explanation for the rise in blood glucose and muscle glycogen content observed in the face of complete inhibition of splanchnic glucose production when large doses of fructose (6–17 mmol/min) are infused.[4] The effect of fructose infusion in raising blood glucose concentration and increasing glycogen storage in muscle[4,5] would thus appear to depend, at least in part, on its stimulatory effects on glucose release by the kidney.

The addition of somatostatin to the fructose infusion resulted in a decline in splanchnic glucose output but failed to alter net renal glucose release. These data thus indicate that the stimulatory effect of fructose on renal glucose output is not dependent on basal glucagon levels. In keeping with these observations, we have previously reported that renal glucose production stimulated by glycerol infusion is not inhibited by somatostatin.[7] In contrast, the inhibitory effect of somatostatin on splanchnic glucose output in the face of fructose infusion is consistent with previous observations that basal levels of glucagon are necessary to maintain splanchnic glucose release in 60-h fasted subjects[24] and in association with infusion of precursors for hepatic gluconeogenesis such as alanine.[7] The contrasting responses of net renal and splanchnic glucose exchange to somatostatin in the face of fructose infusion thus provide further evidence that hepatic and renal gluconeogenesis are regulated by different mechanisms.[7]

In addition to its effects on net renal glucose balance, administration of fructose resulted in a reversal of renal lactate exchange from a significant net uptake in the basal state to a significant net release after fructose infusion. The rate of lactate release could account for 17% of the net uptake of fructose by the kidney. A net release of pyruvate by the kidney was also noted after fructose administration. These observations suggest that some of the fructose extracted by the kidney is metabolized along the glycolytic pathway. It should be noted in this regard that a small but significant rise in arterial lactate levels was observed in the current study in the face of an increase in splanchnic lactate uptake. These observations contrast with the net splanchnic release of lactate observed with infusion of 2 to 5-fold larger doses of fructose.[2–4] Renal rather than hepatic production of lactate thus accounts, at least in part, for the hyperlactatemia induced by small doses of fructose.

The data on renal and splanchnic fructose exchange permit an estimate of the relative importance of the liver and kidney in the disposal of an intravenous load of fructose. Net splanchnic uptake of fructose (0.75 mmol/min) could account for 38% of the administered fructose load. This finding is in close agreement with previous data demonstrating that the liver is responsible for 30–40% of the disposal of intravenously administered fructose.[2,3,5] Assuming a renal blood flow of 1.3 L/min,[7] renal fructose uptake can account for the disposal of approximately 20% of the administered load. It should be emphasized that urinary losses of fructose amount to no more than 1–5% of the administered load even in the face of blood fructose levels 2–3-fold higher than in the present study.[2,3] The current data thus clearly indicate a role for the kidney in addition to the liver as a site of uptake and metabolism of fructose. However, it should be noted that inasmuch as combined renal and splanchnic uptake leaves 42% of the administered fructose load unaccounted for, the current findings are compatible with the conclusion of Bergstrom and Hultman that peripheral (muscle) uptake of fructose is of major importance in the disposal of this hexose.[4]

It should be noted that in contrast to our previous observations in 60-h fasted subjects,[7] a significant net release of glucose by the kidney was not observed in the basal state. This discrepancy may be accounted for by the fact that a much larger group of subjects was examined in our previous study (N = 17) and their mean rate of net renal glucose release was small (0.04 ± 0.01 mmol/min).[7] Thus, while very prolonged (4–6 wk) fasting results in a consistent release of glucose by the kidney,[25] the effects of a 60-h fast are variable. It should also be noted that the A-RV difference for glucose observed after fructose infusion in the current study (−0.17 mmol/L) is three- to sixfold greater than the A-RV observed in the basal state in 60-h fasted subjects in the previous study.[7]

In conclusion, the current findings have demonstrated that fructose administered intravenously is taken up by the kidney as well as the liver and stimulates the release of glucose and lactate by the kidney in 60-h fasted man. The effect of fructose on renal glucose production is not dependent on basal glucagon levels. The kidney thus contributes

to the disposal of fructose and is responsible, at least in part, for the hyperglycemic and hyperlactatemic effects of this hexose.

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