Effects of Carbohydrates on Uric Acid Metabolism

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The rapid infusion of fructose, but not of glucose or galactose, to normal male volunteers produced a 30% rise in serum uric acid. All three hexoses increased the renal excretion of uric acid, phosphate, bicarbonate, and glucose. While only fructose clearly increased uric acid production, all three hexoses appeared to diffusely inhibit renal proximal tubular function. Data are presented that suggest that fructose infusions may concomitantly stimulate the conversion of preformed adenine nucleotides to uric acid while inhibiting de novo uric acid synthesis. Chronic ingestion of a fructose-rich diet did not alter serum or urinary uric acid.

In 1967, Perheentupa and Raivio first reported that rapid fructose infusions induced hyperuricemia and hyperuricosuria in normal children as well as those with hereditary fructose intolerance. A number of subsequent studies dealing with normal adults and gouty subjects have largely confirmed these observations. While it is generally agreed that fructose induces an increase in uric acid production, the evidence bearing out this point has been largely indirect. In vivo and in vitro studies in the rat suggest that the rapid phosphorylation of fructose by the liver depletes that tissue of adenosine triphosphate (ATP) and phosphate (Pi). The resulting de inhibition of 5'-nucleotidase and adenosine deaminase, consequent to the loss of their inhibitors, ATP and Pi, enables the liver to produce more uric acid from preformed purine nucleotides. Support for this mechanism in man has recently been presented by Fox and Kelly. These authors, studying four gouty subjects, observed that in addition to the hyperuricemia and hyperuricosuria, fructose also increased the urinary excretion of total oxypurines, hypoxanthine, inosine and simultaneously depressed erythrocyte phosphoribosylpyrophosphate and ribose-5-phosphate. These data support the concept that the fructose-induced increase in uric acid production results, at least in part, from increased catabolism of preformed purine nucleotides. However, the effect of fructose on the de novo pathway of uric acid synthesis has yet to be explored.

In order to amplify certain aspects of this fructose-induced hyperuricemia and hyperuricosuria, the present investigation reexamined the effects of fructose loading on uric acid metabolism in normal volunteers. Data are presented that suggest that the ingestion of a high-fructose diet, in contrast to acute loading,
does not alter uric acid metabolism. The failure of equimolar amounts of galactose and glucose to cause hyperuricemia suggests a relatively specific role for fructose. The rise in plasma glutamine, found to accompany fructose loading, is discussed in relation to possible alterations in the de novo pathway. Furthermore, evidence is presented that suggests that the fructose-induced hyperuricosuria is due to a combination of an increased renal urate and solute load, in addition to inhibition of renal tubular transport by fructose.

MATERIALS AND METHODS

Fructose infusions were carried out on eight normal male volunteers, aged 23-35 yr. A potential volunteer was rejected if he had a history of gout, diabetes mellitus, nephrolithiasis, cardiovascular, liver, or renal disease. All subjects had a normal serum creatinine, BUN, electrolytes, fasting plasma uric acid, phosphate, and complete blood count. No medications were ingested within the month preceding the study.

Patients were admitted to the Clinical Research Center on the evening prior to the study day. No food was ingested after 10 p.m. Subjects were studied as outlined in Fig. 1. At 7 a.m., intravenous catheters were introduced. All subjects ingested 500 ml of water by 7:30 a.m. and subsequently ingested amounts of water equal to the volume of urine voided. Control urine was collected on the hour by voluntary voiding and control blood on the half hour between 8 and 11 a.m. At 11 a.m. 0.5 g/kg of hexose (fructose, glucose, or galactose) was infused over 15 min as a 20% solution. Urine was collected 15, 30, 60, 120, and 180 min following the start of the infusion. Subjects remained seated throughout the study except when voiding.

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Fig. 1. Outline of the study protocol used for fructose, glucose, and galactose infusions. The shaded area indicates the time of hexose infusion. Abbreviations: CB, control blood samples; EB, experimental blood samples; CU, control urine samples; EU, experimental urine samples.
The effect of a fructose-rich diet on uric acid metabolism was studied using the authors and other laboratory personnel (two of whom had been previously studied with fructose and glucose infusions) as subjects. Although no attempt was made to rigidly control the diet in this out-patient study, all subjects were instructed to maintain their normal diets during the period of study. Morning blood and 24-hr urine specimens were collected for 8 days. The first 3 days served as control. On days 4 through 8 an additional 100 g of fructose were added to the diet. Estimation of the unsupplemented daily dietary intake of fructose indicated that all subjects ingested 25-50 g daily throughout the 8 days of the study. The addition of 100 g of fructose, therefore, represented a two- to fourfold increase in daily fructose consumption.

Uric acid, lactate, and glutamate were analyzed by standard enzymatic methods adapted to either the spectrophotometer or the fluorometer. Glutamine was measured by the method of Welbourne and Balagura-Buruch with minor modifications. Recoveries of uric acid from the blood and urine and of glutamine from plasma ranged from 98%-102%. The remaining chemical analyses were carried out by the routine clinical laboratory.

RESULTS

Experimental points are plotted as percentages of the mean control value. Thus, any point appearing above the 100% line represents an increase of the experimental value above control and vice versa for points falling below the line.

Figure 2 illustrates the response of plasma uric acid and lactate to fructose infusions. As shown, uric acid rises rapidly reaching a peak elevation of approximately 30% above control by 30 min and then returns toward control values but still remains significantly elevated at 3 hr. The mean control plasma uric acid from eight subjects was 5.9 ± 0.3 mg/100 ml. The peak plasma elevation of 30%, therefore, represents an absolute increase of 1.9 ± 0.2 mg/100 ml. Figure 2 also demonstrates the well-known response of plasma lactate to the
infusion of fructose. As shown, the peak elevation of lactate was also reached at 30 min with a return to normal by 120 min. Although the increase of plasma lactate initially paralleled that of uric acid, it is clearly demonstrated that plasma lactate had normalized at a time when uric acid was still elevated.

Both the plasma concentration and the urinary excretion of uric acid rose concomitantly. As shown by the solid line in Fig. 3, the rate of uric acid excretion (mg/min) peaked early but remained elevated for the entire 3 hr of study. The fractional excretion of uric acid represents that fraction of the filtered urate that is actually excreted. An increase in the fractional excretion, therefore, indicates that at any given filtered load, less net tubular reabsorption is occurring, or a change in the tubular handling of urate has taken place. The broken line in Fig. 3 demonstrates that the fractional excretion of uric acid increased in parallel with the absolute increase of urate excretion.

This change in the tubular handling of uric acid could have been due to decreased tubular reabsorption and/or increased secretion. If tubular reabsorption were decreased, one might expect a concomitant decrease in other solutes that are reabsorbed at the same tubular site as uric acid. Figure 4 shows the effect of fructose on the excretion of phosphate, HCO₃⁻, and glucose, substances that are primarily reabsorbed in the proximal tubule along with uric acid. As shown, the renal clearances of phosphate and glucose and the rate of bicarbonate excretion were all increased by fructose infusion. Figure 5 contrasts the urinary solute excretion following fructose loading with that following glucose loading in the same subjects. It is apparent that while both hexoses induce only minor differences in the rates of solute excretion, major differences in the excretion of HCO₃⁻, uric acid and phosphate were found. It is probable that the somewhat greater solute excretion induced by fructose resulted from its greater effect on HCO₃⁻, phosphate, and uric acid excretion.

The de novo synthesis of uric acid requires the utilization of two moles of glutamine for every mole of uric acid synthesized. Therefore, if the rate of de novo synthesis were acutely increased by fructose, one might expect to see the plasma glutamine concentration fall as the uric acid concentration rose. As
Fig. 4. The effect of fructose on the renal clearances of glucose (C glucose) and phosphate (C phosphate) and the excretion of bicarbonate (HCO₃). The points represent the mean (± SEM) change from control in eight subjects.

Fig. 5. Effect of fructose and glucose infusions on the rate of solute excretion. The experimental points indicate the change from control in each study. The mean control solute excretion for each study is noted. R.N.'s E₅ urine specimen was lost.
shown in Fig. 6, this reciprocity did not occur. In fact, fructose, but not glucose, actually increased the plasma glutamine concentration. Glutamine elevation was noted early and remained significantly elevated throughout the study except for period three. Plasma glutamate levels averaged $31 \pm 4 \mu m/liter$ during the control period in four subjects and was not significantly changed by fructose infusions.

To determine whether these observations are specific for fructose, we carried out the same experiments but substituted glucose or galactose for fructose. The circles in Fig. 7 clearly indicate the inability of either galactose or glucose to increase the plasma uric acid. Although both carbohydrates increased the fractional excretion of uric acid, their effects were more transient than those of fructose, lasting only 30–60 min. Similar transient effects on the clearances of glucose and phosphate and on the excretion rate of $\text{HCO}_3^-$ were also noted. The two subjects who failed to show any increase in plasma uric acid with glucose infusions both had previously shown a 30% increase with fructose.
Serum phosphate concentration, while initially showing little response to fructose, later rose and remained significantly higher than the control level during periods three, four, and five (Fig. 8). This elevation of serum phosphate occurred despite a concomitant increase in the renal clearance of phosphate. Figure 8 also illustrates the expected fall in serum phosphate during the infusions of glucose and galactose.

The daily ingestion of 100 g of fructose for 5 days was well tolerated, apart from a mild increase in flatulence and borborygmi. Figure 9 depicts the inability of a high fructose diet to significantly affect either the plasma concentration or the 24-hr urinary excretion of uric acid.

The rapid infusion of fructose caused a rather striking side effect in two subjects. Beginning approximately 5 min after the start of the infusion a mild right upper quadrant and mid-epigastric discomfort developed that became increasingly more painful. The pain became substantial and in one subject radiated into both shoulders and down both arms. Both subjects became pallid and diaphoretic. The pain rapidly subsided within 10 min of discontinuation of the infusion. Electrocardiograms taken throughout the infusion revealed a mild tachycardia and no signs of ischemia. Two of the remaining six subjects experienced only minimal epigastric discomfort, while the other four had no symptoms at all. The same batch of fructose was used in all studies.
Our studies confirm and extend previous observations on the plasma and urinary uric acid response to carbohydrate loading. The hyperuricosuria may result from several possible causes. First, increases in plasma uric acid have been shown to enhance the renal excretion of urate by stimulating uric acid secretion. Second, it is known that expansion of the extracellular fluid volume inhibits proximal tubular reabsorption of HCO₃⁻, glucose, and phosphate as well as uric acid. However, it is unlikely that volume expansion played a significant role in the present study. Subjects received only 150–200 ml of fluid, representing less than 0.3% of their total body weight. Since fructose is very rapidly taken up by the tissues, the infusion fluid distributed itself in a volume approaching that of total body water, thus lessening its effect on extracellular fluid volume. Glucose, however, is taken up less well by the tissues, thus making more of it available to expand the extracellular fluid space. Despite this, glucose did not manifest any greater effect on the kidney than fructose; in fact, its effect was of lesser magnitude and more transient. Third, it is possible that the solute diuresis subsequent to the carbohydrate infusion caused the increased renal clearance and fractional excretion of uric acid. However, it was shown that the striking increase in the clearances of uric acid and phosphate and the excretion of HCO₃⁻ were associated with only minor changes in solute excretion following fructose infusion. Glucose infusions, while causing similar degrees of solute diuresis, had much less effect on tubular transport. Therefore, we concur with Fox et al. that carbohydrate infusions inhibit renal tubular transport by means other than solute diuresis or volume expansion.

Table 1 lists the various mechanisms by which hyperuricemia may be induced. A significant fall in the rate of urate excretion by the kidney or gastrointestinal tract will result in hyperuricemia. Since fructose-induced hyperuricemia occurs in the face of an increased renal excretion of uric acid it is obvious that a renal mechanism cannot be implicated. The minimal absolute increase in uric acid accumulation secondary to fructose loading can be obtained by adding the product of the extracellular fluid volume (estimated to be 20% of the total body weight) and the change in plasma uric acid concentration to the increased amount of uric acid excreted. As originally suggested by Perheentupa and Raivio, the amount of uric acid that accumulates secondary to fructose loading far exceeds that which could be accounted for by even complete cessation of gastrointestinal excretion.
From the data of Wyngaarden et al., Benedict et al., and Scott et al., one can calculate that in normals, approximately 35%–40% of the total miscible pool of uric acid resides outside of the extracellular fluid space. Assuming that all our normal subjects had both a normal pool size and distribution during the control period, they would have had to shift approximately 90% of their non-extracellular urate into their extracellular pool in order to account for the increment in uric acid seen with fructose loading. It is unlikely that such large shifts would occur so rapidly. We are left, therefore, with the conclusion that fructose-induced hyperuricemia results from an increased rate of synthesis.

Increased uric acid production occurs by either an increase in de novo synthesis and/or an increased degradation of preformed purine nucleotides. Since little direct evidence has been presented that would allow one to choose between these two alternatives, it is possible that fructose stimulates one or both pathways. As Fox and Kelley have pointed out, however, even the most potent stimulator of de novo synthesis, 2-ethylamino-1,3,4-thiadiazole, requires 24–48 hr to cause hyperuricemia. The ability of fructose to induce hyperuricemia within 15 min, suggests that it is not acting on the de novo pathway. Furthermore, we would suggest that fructose may actually inhibit de novo synthesis. Animal studies have shown that fructose loading causes an early and sustained elevation of hepatic inosine monophosphate (IMP) and a later rise in inorganic phosphate (Pi). Both IMP and Pi are known inhibitors of 5-phosphoribosylaminotransferase (PRAT), the enzyme that strongly influences the rate of de novo uric acid synthesis. Thus, if the observed elevation of plasma phosphate actually reflects an elevated hepatic level, and if human hepatic IMP is also increased, then PRAT activity may decrease. Although the rise in plasma glutamine may reflect its increased synthesis or decreased extrahepatic utilization, we would speculate that its elevation results from diminished utilization by an inhibited de novo pathway. Therefore, we concur with previous workers that fructose induces hyperuricemia in man by enhancing the conversion of preformed purine nucleotides to uric acid, and may simultaneously inhibit de novo synthesis.

Infusions of galactose or glucose, in contrast to fructose, did not raise the plasma uric acid, but did increase its urinary excretion. The urinary loss was so small, however, that one would not expect measurable changes in plasma urate to result. Simkin using Cebus monkeys, recently postulated that glucose and galactose either increased urate production or altered its distribution, since the renal losses of urate attending the carbohydrate infusions were unassociated with the expected fall in plasma urate. Although the monkeys lost relatively more urate than did our subjects, the expected fall in plasma urate was rather small in most studies, and probably within the limits of error of his assay. Although we cannot rule out a small increase in the production or shift in distribution of urate secondary to glucose or galactose, we conclude that it must be substantially less than with fructose.

While the rapid ingestion of fructose induces hyperuricemia and hyperuricosuria, the ingestion of even larger loads over a 24-hr period is without measurable effect on uric acid metabolism. Since there are data in the literature
suggesting that gouty subjects may mount a greater uric acid response to fructose, we would advise moderation of their dietary fructose. Obviously, more work with gouty subjects is required to explore this point.

Although the chest pain attending the fructose infusions only occurred in two of eight studies, its appearance was quite dramatic. The initial right-upper-quadrant location suggested that hepatic swelling and capsular distension secondary to rapid fructose metabolism might have initiated the pain. The subsequent substernal and precordial location may represent either radiation from the liver or an associated cardiac or mediastinal process (although the electrocardiogram was unchanged). At comparable rates of infusion, Fox et al. noted the development of anxiety and eructation in a single patient, while Bergstrom et al. were forced to discontinue their infusions in two subjects due to nausea and precordial pain. Perheentupa and Raivio failed to find any alterations in the serum glutamic oxaloacetate transaminase with fructose infusions in children, although Goldblatt et al. and Phillips et al. found some rather nonspecific hepatocellular changes in rats given large fructose loads either intraperitoneally or through the mesenteric vein. Bode et al. biopsied human liver at the time of laparotomy both before and after rapid fructose infusions. Striking decreases in the hepatic concentration of ATP and total adenine nucleotides were noted. The exact clinical meaning of these findings is not yet clear. Both subjects in the present study who developed this painful syndrome have remained in perfect health during the ensuing 18 mo.

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REFERENCES

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