

Comments in Biochemistry

Fructose Metabolism

IV. Enzyme Deficiencies: Essential Fructosuria, Fructose Intolerance, and Glycogen-Storage Disease¹

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ESSENTIAL FRUCTOSURIA is due to a deficiency of hepatic fructokinase, as established by the failure of homogenates of liver to take up U-¹⁴C-fructose (1, 2). Dietary fructose is absorbed but not metabolized by the liver and consequently appears in the urine (3, 4). The condition is benign and the individual with essential fructosuria is asymptomatic despite the fructosuria. The urine gives a positive test for reducing sugar (3, 4). An oral fructose tolerance test gives blood fructose values of 25 mg/100 ml or higher as compared to normal values of 15-25 mg/100 ml (4-7). About 10-20% of the administered dose is excreted in the urine in the patients whereas only 1-2% is excreted by normal individuals (3). After oral or intravenous fructose administration blood lactate and pyruvate become elevated in normal subjects but not in individuals with essential fructosuria (2, 6, 8). D-Sorbitol is converted to fructose, but a larger fraction of this fructose is excreted in the urine (5). Fructose infusion in normal subjects leads to hyperuricemia but not in essential fructosuria (9).

Fructose intolerance is the result of a deficiency of hepatic phosphofructoaldolase that converts fructose-1-phosphate into

D-glyceraldehyde and dihydroxyacetone phosphate (10-17). It has been suggested that a defect in one of the two hepatic aldolases (18) is present in fructose intolerance (12). Dietary fructose is converted to fructose-1-phosphate, which accumulates (19, 20) and is thought to act as a competitive inhibitor of various enzymes (13, 21, 22) resulting in hypoglycemia (14-16, 23-26). The various symptoms of tremulousness, sweating, and vomiting are the result of the hypoglycemia which, if profound, can cause confusion, hypotension, coma, convulsions, cyanosis, and, in infancy, death. Severe hypoglycemia may be produced with an oral fructose tolerance test (14-16, 23, 26, 27). Repeated episodes may result in albuminuria, amino aciduria, hepatomegaly, jaundice, cirrhosis, and physical and mental retardation (14-16, 23, 28, 29). The disease may present in diverse fashion: neonatal jaundice, persistent vomiting with failure to thrive, hepatomegaly, and dislike for school meals (30). Symptoms in infants typically start after weaning (14, 15), and in some cases weaning may be difficult to accomplish because of the aversion to sweetened food. The treatment consists of intravenous glucose in the acute stage (14, 26) and exclusion of fructose from the diet (14, 16, 23, 26, 28, 30, 31). The symptoms tend to be severe in young infants whereas older

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children often are symptomless (13, 24, 25). Members of the family may be affected to different degrees. Many if not all of the patients have a strong aversion to fructose-containing foods (14-16). It is of interest that the teeth of these patients have been reported to be remarkably free of caries (14, 26).

During acute episodes of hypoglycemia induced by fructose, serum phosphorus (14, 15, 26) and serum potassium decrease (14), and serum magnesium and transaminase increase (15). Fructose administration leads to decreased plasma insulin (26, 29) or insulin-like activity (14), hyperuricemia (9), and increased lactate and pyruvate levels (16, 26). Lactate, however, does not always increase (14). Granulocytosis and eosinopenia occur while the liver increases in size (16). A galactose infusion can relieve the fructose-induced hypoglycemia (26) but not in every case (32). As blood glucose levels fall plasma growth hormone rises (26). D-Sorbitol leads to hypoglycemia while L-sorbose has no effect (14, 15, 31). Dihydroxyacetone given after fructose produced a greater and longer lasting elevation of its own level in the blood than when given alone. Such an increased level was not seen in normal subjects (32). The hypoglycemia is believed to be due to decreased release of glucose from the liver (14). During fructose-induced hypoglycemia the patients do not respond to glucagon (16, 26, 32).

Red blood cells and white blood cells normally lack fructokinase and fructose-1-phosphate aldolase activity. The patients' cells metabolize fructose as do normal cells (14). Liver tissue from patients metabolized only 4-6% of U-¹⁴C-fructose to ¹⁴CO₂ and only 1-6% to glycogen as compared to normal human liver (14). Normal human mesenteric adipose tissue can use fructose actively without any inhibition by glucose. These data led to the suggestion that peripheral fat tissue can utilize that portion of a fructose load

which does not seem to be assimilated by the liver (14). The decreased utilization of fructose by the liver is reflected by the fructosuria which occurs following a fructose tolerance test (26).

The hepatomegaly of fructose intolerance may be due to an accumulation of lipids (16, 28). Non-esterified fatty acids in the plasma rise more than twofold after fructose administration in patients but not in healthy subjects (16, 26, 33).

Renal tubular acidosis (34) and a Fanconi-like syndrome with renal tubular reabsorptive defects (35, 36) have been reported to occur in fructose intolerance. The renal tubular acidosis was persistent despite restriction of dietary fructose while the Fanconi-like syndrome occurred only with the administration of fructose and was reversible. The absence of fructose-1-phosphoaldolase has been demonstrated in human renal cortex of patients with fructose intolerance (37). The disturbance in kidney function may be due to the accumulation of fructose-1-phosphate in the renal cortex rather than to the hypoglycemia.

Vomiting is usually attributed to the hypoglycemia that results from fructose ingestion but it has been suggested that it is due to the accumulation of fructose-1-phosphate in the gastrointestinal epithelial cells (26). Gastrointestinal symptoms are not relieved by intravenous glucose although the hypoglycemic symptoms are reversed (26). However, phosphofructoaldolase deficiency has not been described in the small intestinal mucosa by direct enzyme assay. A variant of fructose intolerance has been described in which galactose caused hypoglycemia (38). In this case the red blood cell uridyl transferase was normal. Other patients with fructose intolerance do not develop hypoglycemia after galactose administration (16, 26).

The exact mechanism whereby fructose-1-phosphate accumulation leads to hypoglycemia is not clear. It has been suggested that increased insulin release secondary to

elevated fructose levels causes hypoglycemia (15, 38). However, low or normal levels of plasma insulin have been found during the hypoglycemia (14, 26, 29). In three cases of fructose intolerance an increase in hepatic glucose-6-phosphatase activity was found (39). Fructose-1-phosphate has been reported to inhibit phosphoglucomutase (21). Other studies have shown little if any inhibition of phosphorylase, glucose-6-phosphatase, or phosphoglucomutase (11, 22). The lack of inhibition of phosphoglucomutase by fructose-1-phosphate is consistent with the finding that galactose can raise blood glucose during fructose-induced hypoglycemia (26). It has been shown, however, that fructose-1-phosphate is a competitive inhibitor of glucose phosphate isomerase in the conversion of fructose-6-phosphate to glucose-6-phosphate but does not interfere with the conversion of glucose-6-phosphate to fructose-6-phosphate (22). Perhaps fructose-6-phosphate increases secondarily to the accumulation of fructose-1-phosphate and the fructose-6-phosphate inhibits the enzymes necessary for blood glucose production by the liver.

Galactosemia and fructose intolerance have occurred in the same patient (29). This fortuitous situation was employed to show that the insulin output from the pancreas occurred only with glucose but not with galactose or fructose.

In newborn infants a rapid infusion of fructose caused a prompt but transient decrease in blood glucose concentration (40) especially in infants less than 6 hr of age. Fructose also suppressed the rise in blood glucose induced by the administration of epinephrine and glucagon. It was suggested that a maturation or adaptation of fructokinase or fructoaldolase, or both, occurs in the liver of the newborn infant. A similar result is seen in the newborn calf (41).

Fructosuria may occur in severe liver disease (42). This must be kept in mind where fructosuria after an oral fructose

tolerance test is used as an index of patency of a portocaval anastomosis.

Glycogen-storage disease of muscle due to a deficiency of muscle phosphofructokinase has been described (43, 44). These patients presented a picture indistinguishable from that of phosphorylase deficiency of muscle (McArdle's syndrome or glycogen-storage disease of muscle, type V) (45, 46). These patients tolerated light exercise but not a sudden increase in exertion. Ischemic exercise gave no rise in venous lactate levels that ordinarily would have been expected to occur. In one report (44) antibody to purified normal human muscle phosphofructokinase failed to detect the presence of any structurally related but enzymatically inactive protein. Red blood cell phosphofructokinase was decreased in the patient and in the red blood cells of both parents (44). Interestingly enough, no hemolytic process was present. In another report (43) glycogen synthetase and uridine diphosphoglucose pyrophosphorylase were increased. The increased concentration of glycogen in the muscle was thought to be due to increased synthesis as well as decreased utilization. Phosphofructokinase is microsome bound in frog muscle and is inhibited strongly by calcium ions (47). Because the phosphofructokinase is associated with microsomal membranes as well as being soluble it would be important to characterize both forms of the enzyme in any deficient state. The release of calcium from the sarcoplasmic reticulum to initiate muscular contraction (48, 49) might release phosphofructokinase inhibition and permit glycolysis thus helping to replenish microsomal ATP levels which might be needed to transfer calcium back into the microsomal membrane at the end of contraction (50, 51). If calcium ions do not inhibit soluble phosphofructokinase, then, as the calcium leaves the microsomal membranes, glycolysis will occur since calcium activates phosphorylase (52, 53). Thus contraction

of muscle would be geared to glycogen breakdown and replenishment of ATP in both soluble and microsomal phases. Since these patients can participate in light exercise, but not severe exertion, it would seem that the defect is primarily in white muscle which is a predominantly fast-contracting muscle as compared to red muscle which is a predominantly slow-contracting muscle (54-58). In mammals, muscle consists of a mixture of both red and white muscle fibers (59, 60). Phosphofructokinase activity is quite high in the white muscle of rat, hamster, and rabbit (61).

It is of interest that in Tay-Sachs disease there is a deficiency of fructose-1-phosphate aldolase (62, 63). Because of the marked biochemical derangements that occur in fructose intolerance following fructose administration, the effects of a fructose tolerance test were studied in three patients with Tay-Sachs disease (63). No hypoglycemia, decrease in serum phosphate, or increase in serum magnesium occurred. The relationship of the decreased level of fructose-1-phosphate aldolase to the pathogenesis of Tay-Sachs disease is unknown. The serum fructose-1-phosphate aldolase level is markedly depressed in the homozygous state and only moderately depressed in the heterozygous state and thus can be used to detect early cases, atypical cases, and carrier states (64).

In human hepatomas (65) the ratio of fructose-1,6-phosphate aldolase activity to fructose-1-phosphate aldolase activity was found to be 5.48 ± 1.17 for eight such hepatomas as compared to a ratio of 1, or near 1, in normal adult human liver, in the liver of a patient with benign fructosuria, and in the livers of patients with toxic or viral hepatitis. In postmortem human liver the ratio was not different. In fetal human liver the ratio of aldolase activities was 2 or 3 and 1.63 ± 0.21 in cirrhosis of the liver. In fructose intolerance (four patients) the ratio was between 4.6

and 6.7. In an experimental ascites hepatoma transplanted to adult Wistar rats, the ratio was between 20 and 50 as compared to a ratio of 1, or near 1, in normal adult rat liver and a ratio of 2 to 3 in fetal rat liver. These data suggest that fructose-1-phosphate aldolase and fructose-1,6-phosphate aldolase are distinct despite the fact that each enzyme can utilize both fructose-1-phosphate and fructose-1,6-diphosphate as substrates.

REFERENCES

- SCHAPIRA, F., G. SCHAPIRA AND J.-C. DREYFUS. La lesion enzymatique de la fructosurie benigne. *Enzymol. Biol. Clin.* 1: 170, 1961-1962.
- BAYLON, H., F. SCHAPIRA, R. WEGMANN, J.-C. DREYFUS, R. MOULIAS, C. POYART AND P. COUMEL. Note preliminaire sur l'etude clinique, biologique, histochemique et enzymatique de la fructosurie familiale essentielle. *Rev. Franc. Etudes Clin. Biol.* 7: 531, 1962.
- SACHS, B., L. STERNFELD AND G. KRAUS. Essential fructosuria: its pathophysiology. *Am. J. Diseases Children* 63: 252, 1942.
- MARBLE, A. Diagnosis of less common glycosurias, including pentosuria fructosuria. *Med. Clin. N. Am.* 31: 313, 1947.
- SILVER, S., AND M. REINER. Essential fructosuria: report of 3 cases with metabolic studies. *Arch. Internal Med.* 54: 412, 1934.
- EDHEM, F. ERDEN AND K. STEINITZ. Etudes sur un cas de levulosurie essentielle. *Acta Med. Scand.* 97: 455, 1938.
- STEINITZ, H. Untersuchungen zur Pathologie des Fructose-Stoffwechsels: reine Fructosurie bei Beschwistern: Diabetes und Fructose-Stoffwechsel. *Gastroenterologia* 64: 334, 1939.
- STEINITZ, H., K. STEINITZ AND O. MIZRACHI. Essentielle Fructosurie: Untersuchungen des intermediaren Stoffwechsels bei intravenoser Fructose-belastung. *Schweiz. Med. Wochschr.* 93: 756, 1963.
- PERHEENTUPA, J., AND K. RAIVIO. Fructose-induced hyperuricemia. *Lancet* 2: 528, 1967.
- WOLF, H. P., AND E. R. FROESCH. Uber Aldolase. 4. Enzymaktivitaten in der Leber bei hereditarer Fructoseintoleranz. *Biochem. Z.* 337: 328, 1963.
- NIKKILA, E. A., O. SOMERSALO, E. PITKANEN AND J. PERHEENTUPA. Hereditary fructose intolerance, an inborn deficiency of liver aldolase complex. *Metab. Clin. Exptl.* 11: 727, 1962.
- SCHAPIRA, F., AND J.-C. DREYFUS. Hepatic aldolase in fructose intolerance. *Rev. Franc. Etudes Clin. Biol.* 12: 486, 1967.

13. FROESCH, E. R., A. PRADER, H. P. WOLF AND A. LABHART. Die hereditäre Fructoseintoleranz. *Helv. Paediat. Acta* 14: 99, 1959.
14. FROESCH, E. R., H. P. WOLF AND H. BAITSCH. Hereditary fructose intolerance: Inborn defect of hepatic fructose-1-phosphate splitting aldolase. *Am. J. Med.* 34: 151, 1963.
15. LEVIN, B., V. G. OBERHOLZER, G. J. A. I. SNODGRASS, L. STIMMLER AND M. J. WILMERS. Fructosaemia. An inborn error of fructose metabolism. *Arch. Disease Childhood* 38: 220, 1963.
16. PERHEENTUPA, J., E. PITKANEN, E. A. NIKKILA, O. SOMERSALO AND J. HAKOSALO. Hereditary fructose intolerance. A clinical study of four cases. *Ann. Paediat. Fenniae* 8: 221, 1962.
17. HERS, H. G., AND G. JOASSIN. Anomalie de l'aldolase hépatique dans l'intolérance au fructose. *Enzymol. Biol. Clin.* 1: 4, 1961.
18. RUTTER, W. J., B. M. WOODFIN AND R. E. BLOSTEIN. Enzymic homology. Structural and catalytic differentiation of fructose diphosphate aldolase. *Acta Chem. Scand.* 17: 226, 1963.
19. PITKANEN, E., AND J. PERHEENTUPA. Ein biochemisches Studium über zwei Fälle von Fructoseintoleranz. *Ann. Paediat. Fenniae* 8: 236, 1962.
20. MILHAUD, G. Technique nouvelle de mise en évidence d'erreurs congénitales du métabolisme chez l'homme. *Arquiv. Brasil. Endocrinol. Metabol.* 13: 49, 1964.
21. SIDBURY, J. B. Zur Biochemie der hereditären Fructoseintoleranz. *Helv. Paediat. Acta* 14: 317, 1959.
22. ZALITIS, J., AND I. T. OLIVER. Inhibition of glucose phosphate isomerase by metabolic intermediates of fructose. *Biochem. J.* 102: 753, 1967.
23. FROESCH, E. R., A. PRADER, A. LABHART, H. W. STUBER AND H. P. WOLF. Die hereditäre Fructoseintoleranz, einer bisher nicht bekannte kongenitale Stoffwechselstörung. *Schweiz. Med. Wochschr.* 87: 1168, 1957.
24. DUBOIS, R., H. LOEB, H. A. OOMS, P. GILLET, A. BARMAN AND A. CHEMPENOIS. Etude d'un cas d'hypoglycémie fonctionnelle par intolérance au fructose. *Helv. Paediat. Acta* 16: 90, 1961.
25. PERHEENTUPA, J., AND E. PITKANEN. Symptomless hereditary fructose intolerance. *Lancet* 1: 1358, 1962.
26. CORNBLOTH, M., I. M. ROSENTHAL, S. H. REISNER, S. H. WYBREGT AND R. K. CRANE. Hereditary fructose intolerance. *New Engl. J. Med.* 269: 1271, 1963.
27. CHAMBERS, R. A., AND R. T. C. PRATT. Idiosyncrasy to fructose. *Lancet* 2: 340, 1956.
28. JEUNE, M., E. PLANSON, J. COTTE, S. BONNEFOY, J.-L. NIVELON AND J. SROSOWSKY. L'intolérance héréditaire au fructose: A propos d'un cas. *Pédiatrie* 16: 605, 1961.
29. SAMOLS, E., AND T. L. DORMANDY. Insulin response to fructose and galactose. *Lancet* 1: 478, 1963.
30. BLACK, J. A., AND K. SIMPSON. Fructose intolerance. *Brit. Med. J.* 4: 138, 1967.
31. WOLF, H., D. ZSCHOCKE, F. E. WEDERMAYER AND W. HUBNER. Angeborene hereditäre Fructoseintoleranz. *Klin. Wochschr.* 37: 693, 1959.
32. GENTIL, C., J. COLIN, A. M. VALETTE, D. ALGILF AND M. LELONG. Investigation of carbohydrate metabolism in hereditary intolerance to fructose: Attempt at interpretation of hypoglycemia. *Rev. Franc. Etudes Clin. Biol.* 9: 596, 1964.
33. NIKKILA, E. A., AND J. PERHEENTUPA. Non-esterified fatty acids and fatty liver in hereditary fructose intolerance. *Lancet* 2: 1280, 1962.
34. MASS, R. E., W. R. SMITH AND J. R. WALSH. The association of hereditary fructose intolerance and renal tubular acidosis. *Am. J. Med. Sci.* 251: 516, 1966.
35. MORRIS, R. C. Fructose-induced disruption of renal acidification in patients with hereditary fructose intolerance. *J. Clin. Invest.* 44: 1076, 1965.
36. MORRIS, R. C. Evidence for an acidification defect of the proximal renal tubule in experimental and clinical renal disease. *J. Clin. Invest.* 45: 1048, 1966.
37. MORRIS, R. C., I. UEKI, D. LOH, R. Z. EANES AND P. McLIN. Absence of renal fructose-1-phosphate aldolase activity in hereditary fructose intolerance. *Nature* 214: 920, 1967.
38. DORMANDY, T. L., AND R. J. PORTER. Familial fructose and galactose intolerance. *Lancet* 1: 1189, 1961.
39. HERS, H. G. Augmentation de l'activité de la glucosé-6-phosphatase dans l'intolérance au fructose. *Rev. Intern. Hepatol.* 12: 777, 1962.
40. SCHWARTZ, R., H. GAMSU, P. B. MULLIGAN, S. H. REISNER, S. H. WYBREGT AND M. CORNBLOTH. Transient intolerance to exogenous fructose in the newborn. *J. Clin. Invest.* 43: 333, 1964.
41. EDWARDS, A. V., AND N. POWERS. Effect of intravenous infusion of fructose in newborn calves. *Nature* 214: 728, 1967.
42. KIRSH, M. M., H. CARES AND G. D. ZUIDEMA. Evaluation of the oral fructose test. *Arch. Surg.* 89: 508, 1964.
43. OKUNO, G., S. HIZUKURI AND M. NISHIKAWA. Activities of glycogen synthetase and UDPG-pyrophosphorylase in muscle of a patient with a new type of muscle glycogenolysis caused by phosphofructokinase deficiency. *Nature* 212: 1490, 1966.
44. LAYZER, R. B., L. P. ROWLAND AND H. M. RANNEY. Muscle phosphofructokinase deficiency. *Arch. Neurol.* 17: 512, 1967.
45. McARDLE, B. Myopathy due to a defect in muscle glycogen breakdown. *Cin. Sci.* 10: 13, 1951.

46. HUG, G., J. C. GARANCIS, W. K. SCHUBERT AND S. KAPLAN. Glycogen storage disease, types II, III, VIII, and IX. *Am. J. Diseases Children* 111: 457, 1966.
47. MARGRETH, A., C. CATANI AND S. SCHIAFFINO. Isolation of microsome-bound phosphofructokinase from frog skeletal muscle and its inhibition by calcium ions. *Biochem. J.* 102: 35c, 1967.
48. HUXLEY, A. F. The links between excitation and contraction. *Proc. Roy. Soc., London, Ser. B* 160: 486, 1964.
49. INGELS, N. P., AND N. P. THOMPSON. An electrokinematic theory of muscle contraction. *Nature* 211: 1032, 1966.
50. MAKINOSE, M., AND W. HASSELBACH. Der Einfluss von Oxalat auf den Calcium-Transport isolierter Vesikel des sarkoplasmatischen Reticulum. *Biochem. Z.* 343: 360, 1965.
51. MAKINOSE, M., AND R. THE. Calcium-Akkumulation und Nucleosidtriphosphat-Spaltung durch die Vesikel des sarkoplasmatischen Reticulum. *Biochem. Z.* 343: 383, 1965.
52. MEYER, W. L., E. H. FISCHER AND E. G. KREBS. Activation of skeletal muscle phosphorylase b kinase by Ca^{2+} . *Biochemistry* 3: 1033, 1964.
53. HELMREICH, E., W. H. DANFORTH, S. KARPATKIN AND C. F. CORI. In: *Control of Energy Metabolism*, edited by B. Chance, R. W. Estabrook and J. R. Williamson. New York: Academic, 1965, p. 299.
54. WACHSTEIN, M., AND E. MEISEL. The distribution of histochemically demonstrable succinic dehydrogenase and of mitochondria in tongue and skeletal muscles. *J. Biophys. Biochem. Cytol.* 1: 483, 1955.
55. NACHMIAS, V. T., AND H. A. PADYKULA. A histochemical study of normal denervated red and white muscles of the rat. *J. Biophys. Biochem. Cytol.* 4: 47, 1958.
56. DUBOWITZ, V., AND A. G. E. PEARSE. Reciprocal relationship of phosphorylase and oxidative enzymes in skeletal muscle. *Nature* 185: 701, 1960.
57. BECKETT, E. B. Some applications of histochemistry to the study of skeletal muscle. *Rev. Can. Biol.* 21: 391, 1962.
58. BOCEK, R. M., R. D. PETERSON AND C. H. BEATTY. Glycogen metabolism in red and white muscle. *Am. J. Physiol.* 210: 1101, 1966.
59. NEEDHAM, D. M. Red and white muscle. *Physiol. Rev.* 6: 1, 1926.
60. SRETER, F. A., AND G. WOO. Cell water, sodium, and potassium in red and white mammalian muscles. *Am. J. Physiol.* 205: 1290, 1963.
61. OPTIE, L. H., AND E. A. NEWSHOLME. The activities of fructose-1,6-diphosphatase, phosphofructokinase and phosphoenolpyruvate carboxylase in white muscle and red muscle. *Biochem. J.* 103: 391, 1967.
62. ARONSON, S. M., G. PERLE, A. SAIFER AND B. W. VOLK. Biochemical identification of the carrier state in Tay-Sachs disease. *Proc. Soc. Exptl. Biol. Med.* 64: 4, 1962.
63. SCHNECK, L., G. PERLE AND B. W. VOLK. Fructose tolerance in Tay-Sachs disease. *Pediatrics* 36: 273, 1965.
64. VOLK, B. D., S. M. ARONSON AND A. SAIFER. Editorial: Fructose-1-phosphate aldolase deficiency in Tay-Sachs disease. *Am. J. Med.* 36: 481, 1964.
65. SCHAPIRA, F., J.-C. DREYFUS AND G. SCHAPIRA. Anomaly of aldolase in primary liver cancer. *Nature* 200: 995, 1963.