Comments in Biochemistry

Fructose Metabolism

1. The Fructose Metabolic Pathway

ROBERT H. HERMAN, M.D., AND DAVID ZAKIM, M.D.

The pathways involved in fructose metabolism are shown in Fig. 1. The major source of dietary fructose is sucrose which upon hydrolysis yields equimolar amounts of glucose and fructose. Fructose also occurs in honey and in a large variety of fruits; hence, the name fructose, which means fruit sugar. Absorption of fructose in the small intestine does not seem to occur by an active transport system (1). Dietary fructose in man at the level of 40% of calories in a 3,000-kcal diet causes diarrhea. This is distinct from dietary glucose which can be tolerated at levels of 60–80%. The rat differs from man in this respect in that it can tolerate dietary levels as high as 70% of calories as fructose (2, 3). It is of interest to note that isomaltose, which is a product of the enzymatic hydrolysis of starch and dextrans, is further hydrolyzed by the same enzyme that hydrolyzes sucrose to glucose and fructose (4). Consequently, the names sucrase, invertase, isomaltase, saccharase, β-fructosidase, and maltase 1b are synonymous (4).

The metabolism of fructose appears to be different in different tissues depending on the tissue distribution of the various enzymes involved in fructose metabolism. In the liver the enzyme fructokinase phosphorylates fructose to fructose-1-phosphate (F-1-P), which is then split by fructoaldolase to D-glyceraldehyde and dihydroxyacetonephosphate (DHAP) (5–7). Fructoaldolase has not yet been purified separately from aldolase (8–10) though the existence of the metabolic defect of fructose intolerance (to be discussed in part 3) would suggest that these are different enzymes. Although 1-phosphofructokinase activity has been demonstrated in bacterial systems (11, 12), there is no good evidence that this enzyme is present in mammalian tissue (6). The DHAP produced by cleavage of F-1-P can react with D-glyceraldehyde-3-phosphate (G-3-P) to form fructose-1,6-diphosphate (F-1,6-P). It also can be converted to G-3-P by triosephosphateisomerase or to L-α-glycerophosphate by an NADH-requiring α-glycerophosphate dehydrogenase. This last enzyme is soluble (13). Other non-NADH linked α-glycerophosphate dehydrogenases have been described. The hydrogen acceptor for these enzymes is unknown (14–16), but one purified preparation contained nonheme iron and flavin (17). The physiological significance of these latter enzymes is unknown.

The D-glyceraldehyde can be metabolized by various pathways. A D-triose kinase has been described which can convert D-glyceraldehyde to D-G-3-P (6, 18). L-Glyceraldehyde does not serve as a substrate for this enzyme (6, 18). Glycerokinase (or L-triose kinase (19)) which occurs in liver and kidney but not in skeletal muscle, heart,

1 From the Metabolic Division, U. S. Army Medical Research and Nutrition Laboratory, Fitzsimons General Hospital, Denver, Colorado.
brain, or adipose tissue, phosphorylates glycerol, dihydroxyacetone, and D-glyceraldehyde but not \(\alpha\)-glyceraldehyde (13, 20). From isotopic data the \(\alpha\)-triose kinase seems to be the major path for the further metabolism of \(\alpha\)-glyceraldehyde (21-23). An aldehyde dehydrogenase (7, 25-26) can also convert \(\alpha\)-glyceraldehyde to \(\alpha\)-glyceric acid which can then be metabolized to 2-phosphoglyceric acid by means of the enzyme \(\alpha\)-glycerate kinase (27-30). The 2-phosphoglyceric acid can then proceed to pyruvate or to G-3-P. The \(\alpha\)-glyceraldehyde kinase is present in rat liver, kidney, skeletal and heart muscle, and in horse and beef liver but not in pig liver (27, 29). Half of the rat liver enzyme is mitochondrial (30). There are no data concerning its presence in human liver. \(\alpha\)-Glyceraldehyde can also be converted to glycerol by liver alcohol dehydrogenase analogous to the conversion of acetaldehyde to ethanol.
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(31, 32). Glycerol may also be converted to α-glyceraldehyde by an NADP-requiring aldose reductase (33). But, it is not known to what extent these latter two reactions take place in vivo.

In muscle and adipose tissue hexokinase converts fructose to fructose-6-phosphate (F-6-P) which enters the Embden-Meyerhof pathway (5). The fructokinase content of muscle and adipose tissue seems to be quite low if present at all (34). Muscle contains an NADPH-dependent glycerol dehydrogenase (35) which is lacking in liver.

The handling of fructose by the liver and muscle is insulin independent (36–39), though it has been reported that insulin increases fructose uptake by rat diaphragm in the absence of glucose (40). The fructose uptake by muscle is reported to be quite low (39, 40). Glucose and glucosamine markedly inhibit fructose oxidation by rat diaphragm preparations (40). The interactions of insulin and glucose on fructose metabolism in adipose tissue seem to be similar to that occurring in muscle (41). In contrast, fructose metabolism in adipose tissue seems to be greater than in muscle (41).

In the seminal vesicles and in the lens of the eye, glucose and fructose are interconvertible via sorbitol, the reactions being mediated by aldose reductase and sorbitol dehydrogenase (42–45). An identical interconversion of fructose and glucose with sorbitol as the intermediate seems to take place in peripheral nerve (46–48). This pathway accounts for the presence of fructose in seminal fluid (49). Blood glucose is the source for seminal fructose which could also arise from the dephosphorylation of F-6-P. In ungulates, blood glucose is transformed into fructose in the placenta. In these animals the fetal blood sugar is predominantly fructose and arises from the maternal blood glucose (50, 51).

Sorbitol can be a dietary item occurring in various fruits (cherries, plums, pears, and apples) and is metabolized to carbon dioxide but does not contribute to blood glucose (52). It can be given intravenously, but beyond a certain level in the diet it acts as a cathartic for which it has been used clinically.

The liver can convert fructose into glucose but this occurs by a pathway not involving sorbitol (53). The pathway probably involves the formation of F-1-P followed by cleavage to α-glyceraldehyde and DHAP. The DHAP is converted to G-3-P which reacts with DHAP to form F-1, 6-P and successively F-6-P, G-6-P, and finally glucose. The α-glyceraldehyde would seem to be converted to G-3-P.

References


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