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Disorders of Fructose Metabolism

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- **Three inborn errors are known in the pathway of fructose metabolism. Essential fructosuria is a mild abnormality characterized by the appearance of fructose in the urine after the intake of fructose-containing food.**
- **In hereditary fructose intolerance (HFI), fructose may provoke rapid gastrointestinal discomfort and hypoglycemia upon ingestion, symptoms that may vary from patient to patient and depend on the ingested dose.**

- **Fructose may cause liver and kidney failure when taken persistently, and its intake becomes life-threatening when given intravenously.**
- **Fructose-1,6-bisphosphatase (FBPase) deficiency is also usually considered an inborn error of fructose metabolism although, it is a defect of gluconeogenesis.**
- **The disorder is manifested by the appearance of hypoglycemia and lactic acidosis (neonatally, or later during fasting or induced by fructose) and may also be life-threatening.**

Essential Fructosuria

Genetics

- **The mode of inheritance is autosomal recessive and homozygote frequency has been estimated at 1:130,000. The KHK gene is located on chromosome 2p23.3–23.2.**
- **Tissue-specific alternative splicing results in two isoforms, ketohexokinase A, widely distributed in most fetal and adult organs but with no clear physiological role, and ketohexokinase C, expressed in adult liver, kidney and small intestine, which is affected in essential fructosuria.**

- **Two mutations of the KHK gene, G40R and A43T, both of which alter the same conserved region of fructokinase, have been detected and functionally characterized in a family with three compound heterozygotes.**

Metabolic disorders

Ingested fructose is partly (10–20%) excreted as such in the urine, the rest is slowly metabolized by an alternative pathway, namely conversion into fructose-6-phosphate by hexokinase in adipose tissue and muscle.

Hereditary Fructose Intolerance

- **Three different genes coding for aldolases have been identified. While isozymes A and C are mainly expressed in muscle and brain, respectively, aldolase B is the major fructaldolase of liver, renal cortex, and small intestine.**
- **The human gene for aldolase B (ALDOB) has been mapped to chromosome 9q22.3.**

- **30 mutations of the ALDOB gene have been reported. Among them, three amino acid substitutions, A150P, A175D, and N335K are relatively common among patients of central European and have been detected in 65%, 11% and 8% of mutated alleles, respectively.**

Metabolic Defects

- **HFI is caused by deficiency of the second enzyme of the fructose pathway, aldolase B (fructose 1,6-bisphosphate aldolase), which splits fructose-1-phosphate (F-1-P) into dihydroxyacetone phosphate and glyceraldehyde and converts the triosephosphates into glucose and lactate.**

- **A consequence of the high activity of fructokinase, intake of fructose results in accumulation of F-1-P.**
- **The accumulation has two major effects:**

  (i) Inhibits the production of glucose by blocking gluconeogenesis and glycogenolysis, hence inducing hypoglycemia.

  (ii) Provokes overutilization and hence depletion of ATP, the energy currency of the cell, and of inorganic phosphate, utilized to regenerate ATP.

- **The latter result in an increased production of uric acid, and a series of disturbances, including inhibition of protein synthesis and ultrastructural lesions, which are responsible for the hepatic and renal dysfunction.**
- **The accumulation of F-1-P has also been shown to result in deficient glycosylation of proteins, e.g., serum transferrin, by inhibiting phosphomannose isomerase.**

- **Residual activity measurable with fructose-1,6-bisphosphate as substrate is mainly due to the isozyme aldolase A. Thus, glycolysis and gluconeogenesis are not impaired in the fasted state in HFI patients.**
- **The IV administration of fructose to normal subjects induces the metabolic derangements including the drop in ATP and inorganic phosphate, and rise in urate.**

- **IV fructose results in increased glycemia because of its rapid conversion into glucose. However, the equally rapid conversion of fructose into lactate may provoke metabolic acidosis. For these reasons, the use of fructose, sorbitol and invert sugar has been strongly discouraged for parenteral nutrition.**

Fructose-1,6-Bisphosphatase Deficiency

Fructose-1,6-bisphosphatase (FBPase) deficiency presents in the first 1 to 4 days of life with severe hyperventilation caused by profound lactic acidosis and marked hypoglycemia.

Genetics

- **FBPase deficiency is an autosomal-recessive disorder. Its frequency seems to be much lower than that of HFI; a first estimation of 1:350,000 has recently been reported for the Netherlands. In addition to European and North American patients, many cases have been diagnosed in Japan. The high proportion of Turkish patients might simply be the result of the high rate of parental consanguinity.**

- **There is evidence for the existence of more than one isozyme with FBPase activity in humans. The muscle isoform has different kinetic characteristics to the liver isoform and is not affected in patients with FBPase deficiency.**
- **Only the liver-type isoform gene (FBP1) has been localized to chromosome 9q22.2–q22.3.**

- **22 different mutations have been published. Among them are single nucleotide exchanges, small deletions and insertions, and one gross deletion. All regions of the gene may be affected and, with the exception of the c.961 ins G mutation, which has been reported to be responsible for 46% of mutated alleles in Japan, no single mutation is particularly frequent.**

- **There are several FBPase-deficient patients in whom no mutation could be found affecting the coding region of FBP1. Therefore, it has been supposed that these patients carry mutations within the promoter region of FBP1 or, more hypothetically, in the gene for the bifunctional enzyme which controls the concentration of fructose-2,6-bisphosphate, the main physiological regulator of FBPase.**

Metabolic Disorders

- **Deficiency of FBPase, a key enzyme in gluconeogenesis, impairs the formation of glucose from all gluconeogenic precursors, including dietary fructose. Consequently, maintenance of normoglycemia in patients with the defect is exclusively dependent on glucose (and galactose) intake and degradation of hepatic glycogen. Also, hypoglycemia is likely to occur when glycogen reserves are limited (as in newborns) or exhausted (as when fasting).**