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Hypoxanthine-Guanine-Phosphoribosyltransferase

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Introduction

Intracellular ribonucleotide concentrations were calculated in HGPRT lymphoblasts, fibroblasts, and erythrocytes, as well as in adequate HGPRT controls, to investigate the role of purine ribonucleotides in the regulation of de novo purine synthesis in living human cells deficient in HGPRT. Purine is the second element. Purine ribonucleotide concentrations were not decreased in HGPRT cells, indicating that accelerated purine biosynthesis de novo in HGPRT deficient cells is due to increased abundance of PP-ribose-P rather than altered purine ribonucleotide feedback regulation. HGPRT lymphoblasts and erythrocytes showed dramatic rises in intracellular amounts of certain pyrimidine nucleotides and nucleotide sugars, but not fibroblasts. Measurements of pyrimidine synthesis rates and experimental elevation of intracellular concentrations of PP-ribose-P following incubation of cells with inorganic phosphate refuted the possibility that this abnormality of pyrimidine metabolism was caused by coordinated control of purine and pyrimidine synthesis de novo by PP-ribose-P. Deficiency of hypoxanthine-guanine phosphoribosyltransferase (HPRT) function is an inborn purine metabolism error that causes uric acid overproduction and a wide range of neurological symptoms depending on the severity of the deficiency. In Canada, the prevalence is estimated to be 1/380,000 live births, while in Spain, it is 1/235,000 live births. Overproduction of uric acid is seen in all HPRT-deficient patients and is linked to lithiasis and gout. Extreme movement dystonia, choreoathetosis, ballismus, perceptual and concentration deficits, and self-injurious behaviour are some of the neurological symptoms. Lesch-Nyhan syndrome is the name given to the more extreme cases (patients are normal at birth and diagnosis can be accomplished when psychomotor delay becomes apparent). Patients with partial HPRT deficiency experience these symptoms with varying degrees of severity, although in the least extreme cases, symptoms can be absent. The disorder is also linked to megaloblastic anaemia. HPRT deficiency is inherited in an X-linked recessive manner, so males are normally affected and heterozygous females are carriers (usually asymptomatic). A single structural gene on the long arm of the X chromosome, at Xq26, encodes human HPRT. More than 300 disease-causing mutations in the HPRT1 gene have been discovered so far. Clinical and biochemical studies (hyperuricemia and hyperuricosuria combined with psychomotor delay) as well as enzymatic (HPRT function determination in haemolysate, intact erythrocytes or plasma) findings are used to make the diagnosis. Faster and more precise carrier and prenatal diagnosis is possible with molecular diagnosis. Amniotic cells obtained by amniocentesis at about 15–18 weeks' gestation or chorionic villus cells obtained at about 10–12 weeks' gestation can be used for prenatal diagnosis. Treatment with allopurinol can reduce uric acid production. To prevent xanthine lithiasis, doses must be carefully calibrated. The advancement of useful treatments has been hampered by a lack of precise knowledge of neurological illness. Spasticity and dystonia should be treated with benzodiazepines and gamma-aminobutyric acid antagonists like baclofen if they are present. Physical therapy is recommended, and includes dysarthria and dysphagia treatment, special equipment that help hand function, adequate walking aids, and a body management method to prevent deformities. Self-destructive behaviour requires a mixture of physical constraints, behavioural therapy, and prescription care.

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