

Effects of glutamine deficiency on purine metabolism in the Lesch-Nyhan syndrome. KARI O. RAIVIO and J. EDWIN SEEGMILLER. *Univ. of Calif., San Diego, Calif.*

Glutamine (GLN) is the amino donor in two reactions of *de novo* purine synthesis and in the formation of guanylic from xanthylic acid (XMP). When confluent cultures of fibroblasts from normal individuals or from patients with the Lesch-Nyhan syndrome (LN) are maintained in GLN-free medium for 24 hours, their rate of *de novo* synthesis decreases to one-tenth of control cultures. Addition of GLN causes a 5-15-fold stimulation in both types of cells, but at comparable levels of GLN the rate in LN fibroblasts remains 2-5 times higher than normal. In GLN-free medium, LN cells convert 50% more adenine-¹⁴C to nucleotides than do normal cells. Of the radioactivity taken up, 1.1% is diverted to guanine nucleotide synthesis in the normals, and 2.8% in LN fibroblasts (sum of radioactivity in guanine nucleotides, XMP, the corresponding nucleosides and bases). In GLN-free medium, XMP, xanthosine, and xanthine contain 67% of this total in the mutants and 43% in the normals. Addition of GLN brings about a decrease in the total incorporation into the components of the pathway, but a net increase in guanine nucleotide synthesis, as only 4% of the radioactivity is now found in the xanthine compounds in the mutants and 8.8% in the normals. The results show that the availability of GLN can be rate-limiting not only to *de novo* purine synthesis, but also to guanine nucleotide formation at the XMP aminase reaction. LN cells appear to be more sensitive to GLN deprivation in this reaction, and yet are solely dependent on it for guanine nucleotide synthesis, as they are grossly deficient in hypoxanthine guanine phosphoribosyltransferase activity.

Pyruvic decarboxylase inhibition in ketoaciduria. DERRICK LONSDALE, J. WAIDE PRICE, and RAYMOND J. SHAMBERGER (Intr. by Robert Schwartz). *Cleveland Clinic, Cleveland, Ohio.*

A patient with intermittent episodes of cerebellar ataxia has been described (*Pediat.* 43:1025, 1969). The child excreted large amounts of urinary pyruvic acid during an episode which was studied in detail. Fibroblast tissue culture cells were assayed for pyruvic decarboxylase and found to contain a low concentration of this enzyme. Further examination of urine collected during the ataxic episode revealed that alanine was excreted in amounts proportional to that of pyruvic acid and that both metabolites were in concentrations inversely proportional to those of glutamic acid and aspartic acid. A child with late diagnosed, and hitherto untreated, phenylketonuria (PKU) was examined and found to have a high serum phenylalanine concentration and ketoaciduria. She was treated with a phenylalanine deprivation diet and urines collected in day and night 12-hour contiguous sequence. As the serum phenylalanine concentration fell there was a concomitant decrease in greatly elevated concentrations of urinary pyruvic acid into the normal range together with a steady increase in concentrations of urinary glutamic acid. These observations suggested that inhibition of pyruvic decarboxylase could be an important mechanism in PKU as well as other ketoacidurias and that such a mechanism might involve the metabolism of glutamic acid. Experiments were carried out and showed that authentic α iso caproic acid and phenylpyruvic acid produce a marked decrease in the activity of pyruvic decarboxylase *in vitro*.

Preferential hepatic galactose uptake in the newborn. LAWRENCE F. X. KELLY, RICHARD TRABERT, DAVID ABRAMSON, N. VILDAN

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Previous studies demonstrated impaired carbohydrate tolerance with a delayed and excessive rise in plasma glucose and insulin following oral glucose in healthy full term newborns less than 24 hours of age. To evaluate the role of the liver in determining carbohydrate tolerance, galactose tolerance tests were carried out in 6 full term infants of comparable age. Following a 3 hour fast, galactose (2 gr/Kg) was given by gavage. Blood samples were obtained from umbilical vein and from heel sites before and half-hourly to 3 hours following galactose feeding. Results indicate a rapid rise in total sugar and glucose with an early peak following the galactose feeding with little change in insulin concentration in either umbilical or capillary blood. Paired data analysis revealed a significant difference between total sugar and glucose in umbilical venous blood which was absent in capillary blood. Similarly there was a significant difference between umbilical venous and capillary blood total sugar but no difference in glucose. The data indicate rapid hepatic uptake of galactose as opposed to glucose without change in circulating insulin. The concomitant rise in glucose suggests almost immediate conversion of galactose to glucose in the newborn, which is not seen in older children.

ENDOCRINOLOGY

Idiopathic hypoglycemia—a defect in hypothalamic ACTH-releasing factor secretion. MALCOLM M. MARTIN and ARLINE L. A. MARTIN. *Georgetown Univ. Sch. of Med., Washington, D. C.* (Intr. by Philip L. Calcagno).

Corticotropin releasing factor (CRF) deficiency has not previously been demonstrated as a cause of hypoglycemic convulsions. We have recently studied 3 children who justify such a diagnosis. One child moreover has an identical twin who provided the ideal control in the various test situations. The presence of a disorder in ACTH release was suggested by the absence of a response in plasma cortisol and plasma ACTH to insulin induced hypoglycemia as measured by radioimmunoassay, impaired prompt water diuresis, lack of elevation in urinary 17-OHCS following metyrapone administration despite adequate 11-B-hydroxylase inhibition and normal adrenocortical activation by exogenous ACTH. Normal insulin and growth hormone responses to glucose, arginine, tolbutamide and glucagon administration as well as catecholamine release by insulin induced hypoglycemia confirmed the isolated nature of the defect in keeping with the presence of a normal growth pattern and normal thyroid indices. That the defect is one of hypothalamic activation of ACTH release rather than isolated ACTH deficiency was confirmed by the release of ACTH and rise in plasma cortisol following vasopressin administration. Two children had a history of low birth weight for gestation age. The third infant was born postmature with respiratory distress. The available evidence suggests that this is an acquired defect rather than a genetically determined abnormality. Hypoglycemia due to a defect in hypothalamic activation of ACTH release may provide the explanation for fasting hypoglycemia and convulsions in children otherwise unexplained or masquerading as ketotic hypoglycemia.

A new hypoglycemic syndrome: Fasting and reactive hypoglycemia, normal growth and deficient plasma growth hormone