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Cytosolic acetoacetyl-CoA thiolase deficiency.

3-Oxoacyl-CoA thiolase occurs in 3 forms: 2 mitochondrial enzymes, 1 specific for acetoacetyl-CoA and 1 specific for 3-oxoacyl-CoA derivatives of higher chain length and 1 cytosolic enzyme, specific for acetoacetyl-CoA. It has been suggested that the mitochondrial acetoacetyl-CoA thiolase is involved in ketone body generation while the cytosolic enzyme participates in ketone body utilization. The present study concerns a patient with partial cytosolic acetoacetyl-CoA thiolase deficiency. The patient developed apparently normal during the first 2 months of life, but deteriorated rapidly during the following months. At the age of 12 months she showed hyperkinetic choreatic movements. At the age of 20 months she did not show voluntary movements and was deeply mentally retarded. Blood lactate and pyruvate were both increased, but the ratio was lower then normal (4.8 versus 11.7 for normal). She became extremely ketotic upon fasting and on a ketogenic diet. Thiolase activities of a needle liver biopsy were seperated by column chromatography on DEAE-cellulose according to Middleton (Biochem.J.132 (1973) 717). A low activity of the cytosolic acetoacetyl-CoA thiolase activity (14 n moles/min x mg protein versus 39 n moles/min x mg protein for normal liver) was found. A further kinetic analysis of the residual activity revealed an increased K_m for acetoacetyl (18 µM versus 8 µM for normal liver at infinitely low CoA) and an increased sensitivity for inhibition by CoA.

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Hyperlysinemia as an early symptom of the "ketotic hyperglycinemia" syndrome.

Significant hyperlysinuria, pipecolic aciduria, hyperlysinemia and hyperammonemia were found in two unrelated infants presenting with severe muscular hypotonia and somnolence in the first weeks of life. In the first patient there was no acidosis, whereas in the second acidosis paralleled hyperammonemia. Lysine intolerance was excluded in the first patient by a normal response to a lysine load. The amino acid pattern in urine/plasma of both patients was not compatible with a primary defect in the urea cycle. Further studies revealed that the first patient suffered from methylmalonic acidemia, the second from propionic acidemia. The typical massive hyperglycinemia appeared only a few weeks later in the course of their disease. Defects leading to the "ketotic hyperglycinemia syndrome" should therefore be included in the differential diagnosis of early hyperlysinemia as in such cases a prompt reduction of protein intake may be of vital importance.

84 G M KOMROWER*, I B SARDHARWALLA* and J E COUTTS* (Intr. by H K A Visser).
Willink Biochemical Genetics Unit, Royal Manchester Children's Hospital, Manchester, England. Maternal Phenylketonuria.

Six PKU mothers and their 14 children will be described, with details of their health and intelligence. Three mothers were detected during pregnancy, one woman on two occasions, the first pregnancy being terminated at 18 weeks; dietary treatment was introduced in the other instances. Plasma from mother and foetus, and foetal brain and liver were studied. Full details of the diet will be given with information concerning the increased PHE requirement as pregnancy progresses and the need for careful monitoring of the plasma tyrosine levels. The plasma amino acid levels during the pregnancy were maintained within normal levels and nutrition as exemplified by normal weight gain, haemoglobin and plasma-protein levels together with the general condition of the patient was good. Information concerning the amniotic fluid amino acid concentrations and the plasma phenylalanine and tyrosine levels of the mother and baby at birth will be given. The subsequent progress of the babies born varied, but it is evident that with good motivation, satisfactory dietary control of the pregnant PKU mother is possible and that this has great relevance now many well-treated PKU girls are reaching adolescence and marriageable age.

85 F.K. TREFZ*, D.J. BYRD*, H. SCHMITT* and P.LUTZ (Intr. by H. Bickel). University Childrens Hospital, Heidelberg, G.F.R. In Vivo Study of Heptadeutero-Phenylalanine Metabolism in Phenylketonurics and Hyperphenylalaninaemics.

A method was developed for the determination of deuterated phenylalanine (Phe) and tyrosine (Tyr) in plasma after intravenous loading with heptadeuterated Phe (0.030 g/kg). Phenylthiohydantoinderivatives of the amino acids are formed and separated preparatively by High Pressure Liquid Chromatography. The ratio of deuterated and nondeuterated amino acids is determined by mass spectrometry. Metabolites in urine fractions are investigated by gaschromatography/mass spectrometry. Thus far blood profiles (0-24 hrs) of labelled Phe and Tyr have been established in one control, two hyperphenylalaninaemics and two phenylketonurics. Significant differences were observed between plasma profile of deuterated Phe of control and patients. Extensive hydroxylation of Phe could only be seen in the control. None of the common urinary metabolites of Phe contained measurable amounts of deuterium. The results are compaired with oral loading tests, residual hydroxylase activity and excretion rates of urinary metabolites.

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Development of the blood-brain barrier to protein : a new concept.

The blood-brain barrier to protein in the foetus and newborn has frequently been suggested to be "immature" thus accounting for the higher level of protein in foetal or newborn csf compared with the adult. The barrier in adult animals of many species has clearly been shown by several authors to be the tight junctions between adjacent cerebral endothelial cells. Ultrastructural observations (thin section and freeze fracture) have shown in 40-60 days gestation sheep and pig foetuses that at a stage when the csf protein is more than 10 times that in the adult the tight junctions of cerebral endothelial cells and also of choroid plexus epithelial cells (the blood-csf barrier) are well formed. Immunoelectrophoresis showed that many of the foetal csf proteins are identical with those in plasma. Dynamic studies in 60 day sheep foetuses using human serum protein detected by immunoassay or isotopically have shown that penetration of certain serum proteins from blood into csf (eg α foetoprotein and transferrin) is much greater than would be expected on the basis of their molecular size. This does not occur later in foetal life. Additional electronmicroscopical evidence indicates that the route of penetration may be transcellular via a tubular system of smooth endoplasmic reticulum. It is suggested that the cerebral endothelial and choroid plexus epithelial cells of the early foetal brain are able to transport certain specific serum proteins from blood into brain and csf.

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Effects of dexamethasone, cyclic AMP and insulin on the activity of the urea cycle enzymes in fetal liver in organ culture.

Hormonal agents are used clinically to accelerate biochemical development and enhance functional maturation of small pre-term newborn infants. Present knowledge in the area of hormonal regulation of enzyme maturation in fetal tissues is still rudimentary and needs much further exploration.

We have studied the effects of dexamethasone and cyclic AMP on the activity of all five urea cycle enzymes in fetal rat liver in organ culture. After 24 and 48 hours in culture, dexamethasone or cyclic AMP produce a 2 to 3 fold increase in the specific activity of carbamyl phosphate synthetase, argininosuccinate synthetase (ASS), argininosuccinate lyase and arginase. Ornithine transcarbamylase is not effected by either agent. The increases in the enzyme activities can be abolished by simultaneous addition of cycloheximide. Preliminary experiments indicate that insulin antagonizes the dexamethasone induced increase of the ASS activity.

Thus, the hormonal stimulation of the five urea cycle enzyme activities is not synchronous. The antagonistic effect of insulin may have clinical relevance