51 O. SIMELL[X], I. SIPILÄ[X] and J. RAJANTIE[X] (Intr. by J. Perheentupa). Children's Hospital, University of Helsinki, Helsinki, Finland. Hyperlysinemia with hyperammonemia and homocitrullinuria.

We studied a male patient (K.L.) aged 5 years, who had had feeding difficulties during infancy after weaning, and was later found to be slightly mentally and motorically retarded. The presenting symptom was speech difficulty with marked dysarthria and dysphasia. The liver and spleen were normal in size, leukocyte and platelet counts have always been normal, as have the liver enzymes and function tests. There was a clear aversion against berries and sweet food, but not against proteins. Plasma lysine was continuously 10-20 times higher than normal, and urinary excretion of lysine and homocitrulline were elevated. Blood ammonia was normal during fast, but moderately increased after meals. In an i.v. L-alanine load, 6.6 mmoles/kg of body weight given in 5 or 90 min, the patient developed marked hyperammonemia (peak values 465 uM and 760 uM, respectively) and vomited. Serum urea rose slowly and less than in the controls. Urinary orotic acid excretion was increased during the hyperammonemia but not on a self-chosen diet. Oral load with L-lysine-HCl, 0.5 mmoles/kg of body weight, caused a normal molar increase in plasma lysine and blood ammonia remained normal. The patient apparently has a new possibly inherited hyperammonemic disease, linked to constant hyperlysinemia and homocitrullinuria.

52 K. ULLRICH[*], R. BASNER[*], V. GIESELMANN[*], G. MERSMANN[*] and K. von FIGURA (Intr. by W. Lenz). Department of Pediatrics, Physiol.-Chem. Institute, University of Münster, Germany. Comparative studies of lysosomal enzyme uptake by cultivated fibroblasts, hepatocytes and non parenchymal liver cells.

Different cultured cell types posses receptors recognizing different carbohydrate moieties on lysosomal enzymes (glycoproteins) for adsorptive endocytosis. By using glycoproteins and sugars as inhibitors and by enzymatic modulation of lysosomal enzymes it could be shown that fibroblasts recognize on lysosomal enzymes terminal mannose 6-phosphate residues whereas non parenchymal liver cells recognize terminal N-acetylglucosamine residues. Hepatocytes recognize galactose, mannose 6-phosphate and possibly mannose/N-acetylglucosamine residues on lysosomal enzymes. As liver is the major organ for lysosomal enzyme uptake from blood a calculation was done on the basis of these experiments to predict the uptake of different lysosomal enzymes by hepatocytes and non parenchymal liver cells after in vivo administration for enzyme replacement therapy. Whereas α-N-acetylglucosaminidase is taken up by hepatocytes to 74 % the bulk of α-mannosidase (85 %) and of ß-hexosaminidase (65 %) is taken up by non parenchymal liver cells. The results show that the cell specific uptake depends on the carbohydrate structure of the enzymes and underlines the need for organ specific targeting of the lysosomal enzymes.

53 DIETERLEN Ph.[*], GRASSET E.[*], DESCHAMPS I.[*], DESJEUX JF., LESTRADET H. Groupe de Recherche sur le Diabète et la Nutrition chez l'Enfant INSERM U 83 et Service de Pédiatrie - Hôpital Hérold 7, Place Rhin et Danube 75935 PARIS.

INVESTIGATION OF INSULIN SENSITIVITY IN 18 CHILDREN STARTING A DIABETES MELLITUS.

In normal subject, during a continuous infusion of glucose (1.15 mmol/min. m2) and insulin (42 mU/min. m2), the endogenous insulin secretion is inhibited ; the mean steady state plasma glucose (SSPG) and insulin (SSPI) levels are achieved after 90 min. The SSPG is of 6.6 mM. It was generally accepted that the SSPG reflects individual insulin sensitivity. 18 children without acidosis starting a diabetes mellitus received such an infusion during 4 hours. Under these conditions SSPG, SSPI and SSPFFA levels are achieved after 120 or 180 min. SSPG level varies from 4.4. to 17.8 mM. SSPI level is of 45 ± 8 uU/ml.

There is no relationship between the SSPG level and SSPI, SSPFFA and acetonuria, between the SSPG level and the baseline value of cortisol, glucagon, alanine, as well as the highest level of C. peptide. The rate of FFA decreases similarly, whatever rate achieved at the SSPG. However there is a correlation ($p < 0.01$) between the SSPG level and the FFA and the triglyceride levels at baseline. These results show that in diabetic children without acidosis, there is a great variability of the insulin sensitivity. The initial levels of the triglycerides and of the FFA are closely correlated to this sensitivity.

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54 J. KNUDTZON[*], A. WINSNES[*], S. ØYASÆTER[*] and I. FOSS[*] (Intr. by O. Trygstad). Pediatric Research Institute, Rikshospitalet, Oslo, Norway.

Stimulation of glucagon secretion in rabbits by a human pituitary lipid-mobilizing factor (LMF) and human growth hormone (hGH).

In our studies on the effect of pituitary polypeptides on carbohydrate metabolism, various doses of LMF and hGH, prepared from frozen human pituitary glands according to Trygstad and Foss (Acta endocr. (Kbh) 58, 295, 1968), were injected intravenously into rabbits. A dose-related increase in pancreas-specific glucagon immunoreactivity was found for both LMF and hGH. In fed rabbits (n=4), given 100 µg LMF, a plasma glucagon increase from 112 ± 10 pg/ml (mean ± SEM) to 470 ± 50 was found 60 minutes after injection. Fasted rabbits (n=4) given 40 µg LMF showed a peak glucagon increase from 131 ± 3 pg/ml to 433 ± 20 after 45 minutes. hGH given to fasted rabbits, in doses of 1 and 2 mg, resulted in a maximal glucagon increase to 308 ± 25 (n=4) and 393 ± 40 pg/ml (n=5) after 45 and 30 minutes, respectively. Similar increases in plasma glucagon were found for hGH prepared by nine other laboratories. Control animals given physiological saline or 2 mg human albumin showed no increased secretion of glucagon. The secretion of insulin was increased by both LMF and hGH in fed animals, whereas fasted animals showed a variable response. No significant changes were observed in blood glucose concentrations.

55 A. MOUFTI[*], C. WEINGARTEN[*], F. PUISIEUX[*], T.T. LUONG[*] and G. DURAND[*] (Intr. by J.F. Desjeux). Laboratoire de Pharmacie Galénique et de Biochimie, Centre d'Etudes Pharmaceutiques, Université de Paris-Sud - France. HYPOGLYCEMIA AFTER LIPOSOMIZED INSULIN IN THE RAT.

The use of liposomes as carriers or vehicules for drugs has been investigated. An interesting feature is the capability, the liposomes have for protecting molecules, for instance their capacity for preventing contact and interaction of labile substances with the gastro-intestinal fluids.

The efforts in these laboratories have centered on insulin as the active ingredient. The liposomes are prepared using a 7 : 2 mixture of dipalmitoylphosphatidylcholine (DPPC) and cholesterol, sonicated for 2 minutes. The non-liposomized insulin is separated out by ultracentrifugation and the liposome fraction then suspended in a pH 7.2 phosphate buffer.

The in vivo effects have been established by intraperitoneal injection into normal male wistar rats. An intraperitonealy administered dose of 0.5 ml of insulin/liposome causes hypoglycemia (54 % of initial blood glucose value) in 9 out of 10 rats in one hour and causes death in 9 out of 10 rats in two hours. When given orally the resulting hypoglycemia is 31 % of the initial value one hour after administration and 50 % after 2.5 hours in 8 out of 10 rats.

The initial results are encouraging and demonstrate the protecting action of the liposomes although there are still problems to be solved.

56 B. FRANCOIS[*], G. WILLEMS[*] (intr. by G. Van den Berghe) Neuropediat. Dept. Université de Louvain, Brussels, Belgium. Use of pemolin in the treatment of the learning disorders in children with phenylketonuria (PKU).

Appropriate dietary management in PKU children was demonstrated to be effective in preventing mental retardation. There is, however, evidence that intellectual functionning is altered to some degree, despite early diagnosis and treatment. Recent reports suggest that PKU children may have impairment of motor-perceptual functionning, short term memory, concentration or attention, linguistic skills and other cognitive deficits which could explain the poor learning performances. Pemolin(amphetamin substitute) has been shown to improve learning difficulties in children with "hyperkinetic behavior". 7 children with classical PKU, 5 to 11 year-old, were selected in this study for their poor academic performance. They had been on diet within 6 weeks of age. Till the age of 5 years, their dietary control was considered good or excellent. The children were examined before and after 6 months of treatment of pemolin (daily dosage ranged between 1.9 and 2.35 mg/kg body weight). The examination included neurodevelopmental and psychoeducational testing (WISC or WPPSI, Bender test, Benton test, Conners' teacher questionnaires).

After treatment a significant score gain was observed in all children (a 20 % to 60 % increase) on tests which involved perceptual skills, short term memory and attention. Long term effectiveness of this treatment is under evaluation.

57 J. MICHELI*, E. STETTLER* and E. JEQUIER* (Intr. by G. Duc) Neonatology, CHUV - Lausanne, Switzerland.

Energy metabolism ($\dot{M}$) and substrate utilisation (SU) in very low birthweight infants (VLB) during the first month of life.

$\dot{M}$ and SU were studied using a new indirect calorimeter which fits into an incubator and allows around the clock measurements. 7 VLB (≤ 1'500 g) were kept under standard nursing conditions in a thermoneutral environment. $\dot{V}O2$ and $\dot{V}CO2$ were continuously measured by a mass spectrometer in an open system. From these data and urinary nitrogen excretion $\dot{M}$ and SU were computed :

Age (days)	$\dot{M}$ ± SEM (W/kg)	% of $\dot{M}$ covered by oxidation of CHO	LIPID	PROTEIN
1- 7	1.96 ± 0.1	73 ± 6	21 ± 5	6 ± 1
8-29	2.26 ± 0.8	82 ± 8	13 ± 8	5 ± 1

It is concluded that with the actual managment of VLB (thermoneutrality, glucose infusion, early feeding) their $\dot{M}$ can be compared to that of healthy term newborns. However, in their extrauterine metabolic adaptation, energy expenditure is mainly covered by carbohydrate oxidation throughout the first month of life, ingested lipids and proteins being spared for storage and growth.