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CARNITINE METABOLISM IN RECURRENT REYE SYNDROME DUE TO DEFECTIVE ACETYL-CoA DISPOSAL. Ingeborg Krieger and Loran L. Bieber. Wayne State Univ. Detroit.

A ten month old infant with multiple Reye Syndrome-like attacks excreted during the illness β -hydroxybutyrate, acetoacetate and large amounts of the following dicarboxylic acids: adipate, suberate, sebacate, ethylmalonate and glutarate. Production of CO_2 from (1- ^{14}C) and (U- ^{14}C) palmitate and (1- ^{14}C) butyrate was 83%, 5% and 50%, respectively. Acyl-CoA dehydrogenase was normal. Riboflavin therapy eliminated the dicarboxylic aciduria under ordinary load conditions. Carnitine metabolism was studied because plasma carnitine was low (22.2 $\mu mol/l$) and continued to decrease despite the apparent beneficial effect of riboflavin. Urinary free and short chain acylcarnitines (SCAC) were initially 17.1 and 108.9 $\mu mol/l$ (N:24.2 and 38.9), suggesting that hypocarnitinemias was due to urinary SCAC-loss (86-96% of total) although absolute losses (227 $\mu mol/g$ cr) were only mildly elevated. Urine values normalized during i.v. glucose. After recovery from the attack and from dicarboxylic aciduria under riboflavin therapy, oral carnitine was given. This unveiled the persistence of the underlying defect, because SCAC excretion increased to 994 $\mu mol/g$ cr. On a beef broth supplemented diet, SCAC excretion was 791-825 $\mu mol/g$ cr. On a low-fat, low-protein diet without beef broth SCAC was 140 $\mu mol/g$ cr. Acetylcarnitine was consistently the major urinary carnitine ester: 1052 nanomol/ml (N:18.9) or 620 $\mu mol/g$ cr. This compares with the acetylcarnitine excretion of adults after 60hrs. starvation and suggests a partial block in the disposal of acetyl-CoA. Reye Syndrome-like attacks may be precipitated by mitochondrial trapping of CoA-SH as acetyl-CoA viz. acylCoA.

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CONTROL OF GLUCONEOGENESIS IN THE BABOON FETUS. Lynne L. Levitsky, John B. Paton, David E. Fisher, Nancy H. Spaulding, and Audrey L. Paton. Pritzker School of Medicine, University of Chicago; Michael Reese Hospital and Medical Center, Department of Pediatrics, Chicago.

Regulation of gluconeogenesis has been studied in 4 baboon fetuses (135-140 d.) with catheters chronically placed in the inferior vena cava and aorta, using a single isotope-labeled precursor technique. A primed infusion of [u- ^{14}C] lactate (Lac) was administered to the fetus to steady state over 150 min. Net Lac to glucose (Glu) conversion was evaluated by comparing fetal (Fet) and Maternal (Mat) dpm and specific activity (S.A.) of Lac and Glu during Mat fed (4), fasting (4), and Glu infusion (1) (Iglu).

	Glu mM	Lac (mM)	Glu/Lac dpm (%)	Glu/Lac SA (%)
Mat Fed	2.60 \pm 0.16	.52 \pm 0.08**	55.3 \pm 1.6*	11.8 \pm 2.5**
Fast	2.26 \pm 0.23	.71 \pm 0.08	65.5 \pm 5.4	44.1 \pm 15.4
Iglu	6.86	1.02	17.8	1.3
Fet Fed	2.02 \pm 0.20	1.36 \pm 0.04	10.9 \pm 1.0*	4.1 \pm 3.3**
Fast	1.73 \pm 0.06	1.86 \pm 0.35	15.3 \pm 2.0	8.7 \pm 1.0
Iglu	5.80	2.81	7.5	1.7

* fed vs. fast p<.05 **fed vs. fast p<.001

Mat/Fet Glu dpm were 36.0 \pm 1.9% fed, 51.4 \pm 3.1% fasting (p<.001) and 9.2% during Iglu. Mat/Fet Glu S.A. was 27.6 \pm 2.4% fed, 44.7 \pm 5.2% fasting (p<.001) and 9.5% during Iglu. Fet to Mat placental transfer of Glu and Lac is more efficient in the baboon than in the sheep, but higher Fet than Mat ^{14}C Glu enrichment confirms the capacity of the primate fetus for gluconeogenesis. Fet gluconeogenesis from Lac is regulated by Mat nutrient status and substrate supply.

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TRANSIENT NEONATAL DIABETES MELLITUS TREATED WITH INSULIN INFUSION PUMPS AND PANCREATIC BETA CELL FUNCTION FOLLOWED BY URINARY C-PEPTIDE EXCRETION. Louie G. Linarelli, Barry Smith, Heinz Paulus. Children's Hospital, Department of Pediatrics, University of California, San Diego.

JM was a 1928 gram, 36-week small for gestation age male infant born to a Grav.-III, Para-0 mother. Hyperglycemia of 340 mg % was identified on arrival to the nursery. Conventional approach changing from regular to NPH insulin proved unsatisfactory. Thus regular S.C. insulin (U20) was administered every 3 hrs pre-formula feeding based on Glucometer blood heel stick glucose using a sliding scale insulin dosage of 0.1 to 0.5 units. Pen-Pump (U20 regular insulin) was utilized with manual administered pre-meal doses. Insulin syringes were refilled every 12 to 24 hrs and needle sites changed every 2 to 3 days. A trial on CPI Model 9100 ambulatory infusion pump was shown feasible with continuous insulin of 3 units/24 hr rate (U10 insulin). JM was discharged at 1 month of age on a Pen-Pump with home glucose monitoring pre-meals and sliding dose regular insulin. An infusion site staph aureus cellulitis resulted in rehospitalization. A new trial of NPH (U10) b.i.d. proved effective in management by six weeks of age in the range of 2.2 units b.i.d. As the NPH insulin dose decreased from 2.2 U b.i.d. to 0.3 U b.i.d. from 3 to 6 mos. of life, home glucose monitoring, hemoglobin A_{1c} and urine C-peptide were helpful guidelines. Urine C-peptide proved an effective means of following residual pancreatic beta cell function with recovery of diabetes by 6 mos. of age. Timed measured urine samples every 2 weeks showed a rise from nil C-peptide to 4.0 ng/ml with return of pancreatic beta cell function. Urine C-Peptide measured by Immunex Tek-Pharma, Sorrento, Valley, CA

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CARBAMOYL PHOSPHATE SYNTHETASE DEFICIENCY: DNA ANALYSIS. R Mallonee, E Fearon, J Phillips III, W O'Brien, S Brusilow, M Adcock and L Kirby. Depts Peds, Johns Hopkins Univ Sch Med, Baltimore, Baylor College Med, Houston and Children's Hospital, Dept Path, Vancouver, B.C.

Carbamoyl phosphate synthetase deficiency (CPSD) is an autosomal recessive disorder of ureagenesis. Untreated patients with complete CPSD die as neonates of hyperammonemia. Since CPS is not expressed in amniocytes, prenatal detection is limited to in utero liver biopsy. To determine if the CPS genes are abnormal in affecteds we analyzed nuclear DNA prepared from leukocytes or fibroblasts by hybridization to rat and human CPS cDNA sequences. DNAs from 6 individuals affected with CPSD, 2 non-affected sibs and 2 controls were digested with Eco RI, Hind III or Pst I and hybridized to ^{32}P labeled rat CPS cDNA. No variations in the number or size of hybridizing fragments were seen. To enable linkage studies DNAs from the 10 parents were digested with 12 different restriction endonucleases. Only after Bgl I digestion was a variation seen (23,15.5 and 13 kb bands in some versus 23 kb in others). Using a smaller human CPS cDNA we detected three patterns 23, 23+13 and 13 kb. In one family both parents had the 23+13, 2 affected sibs had only the 23 and a normal sib had only the 13 kb fragment(s) in agreement with simple Mendelian inheritance. In 2 other families the affected had only the 23 kb fragment. The affected children in the remaining 2 families had 23+13 or 13 kb patterns. Our studies suggest that 1) large deletions or insertions of the CPS genes were not detected; 2) the CPSD phenotype and the Bgl I derived restriction fragments co-segregate and 3) genetic heterogeneity exists in CPSD.

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HYPERCALCIURIA AND GROWTH FAILURE IN CHILDREN WITH DIABETES. John I. Malone, John A. Duncan, Shirish C. Shah, Nelly Wolff, Dorothy Shulman, Saul Lowitt, Alfonso Vargas, Allen W. Root. Dept. of Pediatrics, University of South Florida, Tampa, Florida.

Growth failure and hypercalciuria have been noted independently in children with insulin-dependent diabetes mellitus (IDDM). We evaluated growth and calcium metabolism in 175 IDDM children and 38 non-diabetic (ND) sibs of similar ages. Height was determined by 2 of the authors using a Stadiometer. Blood and urine were collected in the AM before food and insulin had been taken. Results: (mean \pm SEM) urine calcium/creatinine (Ca/Cr) (ND=0.13 \pm 0.01, IDDM=0.21 \pm 0.01 p<.001), serum Ca (ND=9.7 \pm 0.07 mg/dl, IDDM=9.6 \pm 0.02 mg/dl p=NS), alkaline phosphatase (ND=105.8 \pm 7.0 IU, IDDM 284.9 \pm 7.5 IU p<.001) Vitamin D₃ ND=20.0 \pm 1.8 ng/ml, IDDM=23.0 \pm 2.0 ng/ml p=NS), PTH (ND=140.3 \pm 7.9 pg/ml, IDDM=158.4 \pm 5.2 p=NS), Ht (ND=54 \pm 3.8 percentile, IDDM=43.7 \pm 2.3 percentile p<.05). Ca/Cr correlated with coincident serum glucose r=.28 p<.0002, HbA_{1c} r=.24 p<.0004, but not with serum Ca, alkaline phosphatase, vitamin D or PTH. Ca/Cr correlated inversely with Ht percentile r=.20 p<.01. IDDM with Ca/Cr>ND range were shorter 37 \pm 3.2 percentile than ND 54 \pm 3.8 percentile p<.01. Hypercalciuria was associated with both poor glycemic control and growth failure in IDDM children. When coincident serum glucose, HbA_{1c} and duration of IDDM are factored out of the analysis of variance the Ca/Cr continues to have a negative correlation to height percentile. Hypercalciuria appears to be an important factor in the growth failure associated with IDDM.

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INHIBITION OF FATTY ACID OXIDATION BY SULFONYLUREAS. Kenneth McCormick, Robert Sicoli, Margaret Williams. (Spon. by Gilbert B. Forbes). University of Rochester Medical Center, Dept. of Pediatrics, Rochester, NY.

Sulfonylureas potentiate the cellular action of insulin, not by changing membrane receptor number as previously thought, but by unknown postbinding mechanisms. We investigated the direct effects of tolazamide on fatty acid oxidation in isolated intact liver mitochondria, prepared from fed and fasted rats. Total ketone body formation and CO_2 production (\approx 10% of total oxidative products) were measured using ^{14}C palmitate. Ketogenesis results are expressed in nmols/min/mg prot. (\pm SEM).

DRUG $\mu g/ml$	0	.004	.04	.4	4	40
Fed (10)	2.30 \pm .11	2.33 \pm .20	2.05 \pm .17	1.72 \pm .07	1.61 \pm .12*	1.63 \pm .17
Fasted (10)	2.01 \pm .15	2.00 \pm .18	2.10 \pm .21	2.00 \pm .21	2.00 \pm .15	1.96 \pm .20

*p<.001 vs control. Changes in CO_2 production paralleled those of ketone formation (data not shown). Only mitochondria from fed rats were sensitive to tolazamide inhibition of fatty acid oxidation; this was dose dependent with a maximum attenuation at 4 $\mu g/ml$. Carnitine acyltransferase activity was unaffected by high dose tolazamide.

In the absence of insulin, sulfonylureas, at levels below therapeutic (20-40 $\mu g/ml$), attenuate fatty acid oxidation in hepatic mitochondria from fed rats. This inhibition occurs proximal to acetyl CoA formation; perhaps these compounds are related to or intensify a putative insulin mediator released after receptor occupation.