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**RESPONSE OF WHOLE-BODY LEUCINE METABOLISM TO VARIATION IN PARENTERAL AMINO-ACID INTAKES IN CHILDREN ON PARENTERAL NUTRITION.** O. Goulet, J-J. Robert, M. Rongier, V. Colomb, C. Ricour, J-F. Desjeux, D. Darmaun. INserm U290 et Hôpital Necker-Enfants Malades. Paris. France.

The response of protein turnover to changes in nitrogen (N) intakes was studied in 6 children (8-16 years) on parenteral nutrition (PN). All were on stable nutritional status receiving cyclic home PN for short bowel or CIPO syndrom. Daily PN intakes included 68.7 ±13.0 Kcal/Kg lean body mass (LBM) with 25.4 ±3.6 % lipid (Intralipid 20 %). Non protein energy, water and electrolytes remained unchanged while patients were given for 3 consecutives 7 days periods 0.7, 1.5, 2.5 g of aminoacids (AA) per Kg LBM/day. On day 7 of each period children received a short (4h) constant infusion of L-[1-13C] leucine during IV feeding ; leucine turnover (Ra) and oxydation (Ox) were calculated from 13C-plasma ketoisocaproate and expired 13CO2 enrichments. Non oxydative leucine disposal an estimate of protein synthesis (S) and leucine derived from protein breakdown (B) were calculated. Results : µmol/Kg/LBM/hour Anova * p<0,05 ** p<0,01

| Protein intakes | Ra** | Ox ** | B | S* | S-B* |
|---|---|---|---|---|---|
| 0.7 | 205 ± 14 | 32 ± 9 | 156 ± 18 | 172 ± 17 | 16 ± 9 |
| 1.5 | 291 ± 34 | 82 ± 18 | 186 ± 35 | 209 ± 35 | 22 ± 16 |
| 2.5 | 353 ± 42 | 127 ± 30 | 184 ± 39 | 225 ± 45 | 42 ± 21 |

Increased AA intakes induce a dose dependent rise in leucine Ra and Ox. (S-B) an index of net protein accretion increase with graded N intakes and correlate with N balance which was negative in 2 children at 0.7 gAA/Kg LBM/day. Those results suggest that increasing AA intakes might be beneficial for children on long term PN.

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EFFECT OF MEDIUM CHAIN TRIGLYCERIDE (MCT) ADMINISTRATION ON CARNITINE METABOLISM IN THE ANESTHESIZED PIGLET AND CULTURED KIDNEY EPITHELIAL CELLS. Duna Penn, Andrew Cochrane, Vuong N. Trieu, Dennis D. Black, and Eberhard Schmidt-Sommerfeld. Department of Pediatrics, University of Chicago and Department of Biochemistry, Michigan State University, East Lansing, USA.

To test the hypothesis that carnitine plays a role in medium chain fatty acid metabolism, blood, urine, liver and bile specimens were collected from anesthesized neonatal piglets prior to, and after 30, 60, 120 and 180 minutes of a continuous intravenous infusion of MCT (1 g/kg-h). Interval fractional tubular reabsorption was calculated throughout the infusion. $^{3}$H-L-Carnitine uptake was determined in cultured renal tubular epithelial (Cos-1) cells incubated with increasing amounts of octanoic acid. Results: The ketogenic response to MCT administration was associated with a rise in esterified (15.2-->40.9 µM), particularly acetylcarnitine (11.4-->26.2 µM), and a fall in free carnitine plasma concentrations (34.6-->14.4 µM). The appearance in the plasma, bile and liver of butyryl-, hexanoyl-, octanoyl- and decanoylcarnitine and the greater than 4-fold increase in ratios of plasma free fatty acids/β-hydroxybutyrate and lactate/pyruvate suggested overloading of both β- and Krebs cycle oxidative pathways. The fractional tubular reabsorption of free carnitine decreased from 96.5% to 48.7% with MCT loading, and was associated with a 6-fold increase of free carnitine excretion. Uptake of $^{3}$H-L-Carnitine into Cos-1 cells decreased in a dose-dependent manner with increasing octanoic acid concentration. The results suggest that MCT loading has profound effects on carnitine metabolism affecting intracellular esterifications and renal tubular reabsorption.

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**POSTNATAL KETONE BODY KINETICS IN PRETERM NEWBORN INFANTS DURING GLUCOSE INFUSION.** Eric Sanders, Rienk Baarsma, Albert Okken. Div. of Neonatology, Dept. of Pediatrics, University Hospital, Groningen, The Netherlands.

Gluconeogenesis and ketogenesis are regarded as important for preserving blood glucose homeostasis in human newborns. We have studied simultaneously ketone body (KB) and glucose turnover rates in six preterm newborn infants (gestational age: 33.0 ± 3.6 wk; birth wt: 1937 ± 861 g) 28.7 ± 19.3 h postnatally, during glucose infusion with a rate of 20.5 ± 5.1 µmol/kg.min. Kinetics were measured using [1,2,3,4 $^{13}$C$_4$]acetoacetate, D-(-)-3-OH-[4,4,4 $^{2}$H$_3$]butyric acid and [6,6 $^{2}$H$_2$]glucose. The enrichment of tracers in plasma was analysed by gas chromatography/mass spectrometry. Results: Total KB production rate was 1.90 ± 0.78 µmol/kg.min. The rates of interconversion between acetoacetate and 3-OH-butyrate ranged widely. The whole body glucose turnover and the glucose production rate (GPR) were 30.3 ± 6.8 µmol/kg.min and 9.8 ± 5.8 µmol/kg.min, respectively. In two infants the glucose infusion rate was doubled stepwise during the study and the turnover studies were repeated. Both KB turnover and GPR were reduced. Conclusion: In preterm newborn in the first days after birth the turnover of KB is suppressed, the plasma KB concentration is low, and the contribution to total energy metabolism is negligible during administration of glucose. The regulation of ketogenesis seems to be functioning in these newborn infants.

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**EFFECTS OF A HIGH DIETARY LINOLEIC/ALPHA-LINOLENIC ACID RATIO IN FORMULA FED PREMATURE INFANTS.** B. Koletzko, E. Sulkers*, I. Thiel, J. van Goudoever*, P.J.J. Sauer*. Kinderklinik der Heinrich-Heine-Univ., Düsseldorf, Germany and *Sophia Children's Hospital, Erasmus Univ., Rotterdam, Netherlands

Long-chain polyunsaturated fatty acids (LCP, 20-22 carbon atoms) are important for perinatal growth and development. In contrast to human milk, current infant formulae do not contain LCP. Hence, formula fed infants depend on endogenous LCP synthesis from linoleic (LIN, n-6) and alpha-linolenic (A-LIN, n-3) acids which compete for one enzyme system. We studied whether the dietary LIN/A-LIN ratio affects plasma phospholipid n-6 and n-3 LCP in premature infants. Subjects and methods: 28 premature infants (gest. age 31±2 wks., birthweight 1.2±0.2 kg, M±SD) were fed either a formula with 17.0 % LIN and a LIN/A-LIN ratio of 10, i. e. similar to human milk (control, n=13), or a formula high in LIN (31.7 %) and low in A-LIN (0.3 %) (n=15). Plasma phospholipid fatty acids on day 28 of life were measured with capillary gas-liquid chromatography. Results: Total phospholipid fatty acid concentrations did not differ between groups. Percentage contents of LIN and its n-6 metabolites were higher in the high LIN/A-LIN ratio group, but n-3 fatty acids were similar.

PLASMA PHOSPHOLIPID FATTY ACIDS ON DAY 28 (% WT/WT, M±SE)

| Fatty acid | Control group | High LIN/A-LIN ratio | P value |
|---|---|---|---|
| C18:2n-6 (LIN) | 11.76±0.29 | 13.15±0.26 | =0.0015 |
| C20:4n-6 (AA) | 3.51±0.20 | 4.74±0.33 | =0.0042 |
| Total n-6 LCP | 9.54±0.34 | 11.16±0.42 | =0.0063 |
| C18:3n-3 (A-LIN) | 3.84±0.27 | 3.33±0.10 | n.s. |
| C22:6n-3 (DHA) | 0.84±0.07 | 0.78±0.13 | n.s. |
| Total n-3 LCP | 3.71±0.18 | 3.37±0.29 | n.s. |

Conclusions: Premature infants fed a diet low in n-3 fatty acids maintain phospholipid n-3 fatty acids relatively stable for a short period of time, possibly by utilizing body pools. A high dietary intake of LIN with a large LIN/A-LIN ratio seems to enhance n-6 LCP biosynthesis.

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**MEVALONIC ACIDURIA: IMPAIRED UBIQUINON BIOSYNTHESIS AND MODEL FOR SIDE EFFECTS OF HMG-COA REDUCTASE INHIBITORS.** G. F. Hoffmann, C. Charpentier, K. M. Gibson and C. Hübner. Depts. Pediatrics, Heidelberg, Paris (France) and Hamburg (FRG), and Baylor University Medical Center, Dallas, TX, (USA)

Mevalonic aciduria due to mevalonate kinase deficiency is the first inherited disorder of cholesterol and nonsterol isoprene biosynthesis in man. The metabolic defect is partially counteracted by increased activities of 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase and the low-density-lipoprotein receptor pathway, similar to the pharmacological effects of HMG-CoA reductase inhibitors. In ten patients., we observed psychomotor retardation (10/10), hypotonia/myopathy (9/9), ataxia (5/9), failure to thrive (9/10), recurrent crises with fever/diarrhea (8/9), anemia (7/9), hepatosplenomegaly (5/10), cerebellar atrophy (5/7) dysmorphic features (5/10) and cataracts (3/10). Three patients died. The severe and diverse clinical symptoms are caused by a shortage of different end products. Ubiquinon 10, an important antioxidant, was found to be diminished in tissue samples and plasma of most patients investigated, arguing against the hypothesis that the synthesis of nonsterol isoprenes as compared to cholesterol is safely assured by high affinities of the branch-point enzymes for farnesyl pyrophosphate. The severe multisystemic pathology might be attributed to free radical pathology. Therapeutic interventions with corticosteroids ameliorated the recurrent crises. HMG-CoA reductase inhibitors may impair the biosynthesis of nonsterol isoprenes in a fashion analogous to that observed in mevalonic aciduria

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IMPAIRED DEGRADATION OF LEUKOTRIENES IN PATIENTS WITH PEROXISOMAL DEFICIENCY DISORDERS. Ertan Mayatepek, Gabriele Jedlitschky, Ruud B. H. Schutgens*, Ronald J. A. Wanders*, and Dietrich Keppler. Division of Tumor Biochemistry, Deutsches Krebsforschungszentrum, Heidelberg, Germany, and *Department of Pediatrics, University Hospital, Amsterdam, The Netherlands.

The degradation of leukotrienes (LT) by β-oxidation from the ω-end proceeds in liver peroxisomes (J. Biol. Chem. 266:24763-72, 1991). Peroxisomal LT degradation was studied in man by analyses of endogenous LTs in urines from 9 patients with biochemically established peroxisomal deficiency disorders (PDD) and 9 age- and sex-matched healthy infants. LT metabolites were separated by reversed-phase HPLC and quantified by specific radioimmunoassays.

*Results:* Urinary $LTE_4$ relative to creatinine (nmol/mol ± SD) increased from 59±23 in controls to 590±265 in patients, and N-acetyl-$LTE_4$ from 16±13 to 212±169 nmol/mol, respectively (p<0.01). The β-oxidation product ω-carboxy-tetranor-$LTE_3$ amounted to 48±33 nmol/mol in controls but was lacking in PDD. $LTB_4$ was absent in normal urine but detectable in PDD (86±67 nmol/mol).

*Conclusion:* The impairment of degradation and inactivation of LT in PDD leads to an altered pattern of LT metabolites which is of diagnostic value and possibly of pathophysiological significance.