

### 1195 CARNITINE METABOLISM IS ABNORMAL IN GENETICALLY OBESE (ob/ob) MICE; Paul J. Benke and Jose R. Foradada, University of Miami School of Medicine, Mailman Center and Department of Pediatrics, Miami, Florida

Genetically obese (ob/ob) mice have decreased  $\text{Na}^+\text{K}^+$  ATPase activity, an enzyme that transports carnitine and other small molecules across cell membranes. Free carnitine levels in plasma of ob/ob mice was  $33.0 \pm 2.9$  ( $\pm 1$  S.D.) compared to  $45.6 \pm 2.7$  in their non-obese littermates ( $p < .05$ ). Plasma acylcarnitins were similar in the two groups of animals. Serum levels of carnitine were low because obese animals excrete more carnitine and acylcarnitins in their urine than control animals. [ $^{14}\text{C}$ ]-carnitine uptake from peritoneal fluid was studied in plasma, brown and white adipose tissue and organs. Uptake in ob/ob animals was increased 2 hours after intraperitoneal injection, but depressed at 4 and 6 hours compared to control animals. [ $^{14}\text{C}$ ]-carnitine uptake in brown adipose tissue (BAT) of obese animals was strikingly depressed compared to non-obese animals, but uptake was similar in white adipose tissue, liver and kidneys. Decreased plasma carnitine and almost no carnitine uptake in BAT explain the accumulation of neutral lipids in ob/ob mice, since less carnitine is available to metabolize long chain fatty acids. Altered carnitine metabolism appears to play a role in the obesity and decreased thermal response to stress observed in ob/ob mice.

### 1196 PLASMA AND MUSCLE CARNITINE DEFICIENCY IN RENAL FANCONI SYNDROME. Juan Bernar, Isa Bernardini, William B. Rizzo, Marinos Dalakas, and William A. Gahl. (Spon. by J.B. Sidbury). NIH, NICHD and NINCDS, Bethesda, MD, and Med. Coll. of Virg., D. Peds., Richmond, VA.

Children with renal Fanconi syndrome (FS) fail to reabsorb water, amino acids, glucose, electrolytes, and other small molecules including carnitine. In 21 FS patients (18 with cystinosis, the most common identifiable cause of FS in children), the mean urinary fractional excretions of free and acyl carnitines were 32% and 27%, resp., compared with control values of 3% and 5%, resp. (N=6). Plasma free carnitine was  $11.6 \pm 4.0$  (SD) nmol/ml in FS and  $42.0 \pm 9.0$  in controls ( $p < 0.001$ ). The plasma carnitine deficiency in FS was independent of age, cysteamine therapy, and renal glomerular function. The liver did not appear functionally carnitine-deficient in FS, since 2 patients exhibited a normal, 5 to 10-fold increase in  $\beta$ -hydroxybutyrate and acetoacetate after a 24-hour fast. In 2 other patients with cystinosis and plasma carnitine deficiency, muscle free carnitines were 8.5 and 13.1 nmol/mg noncollagen protein (4 controls  $19.2 \pm 2.5$ ); total muscle carnitines were 11.8 and 13.3 (controls  $24.8 \pm 7.5$ ). The greatest relative decrease in muscle carnitine was in the short chain acyl carnitine fraction. One muscle biopsy in a cystinosis patient revealed an increase in lipid droplets. A muscle biopsy in another patient showed a large increase in lipid droplets, small vacuoles, occasional "ragged-red" fibers, a slight increase in connective tissue, and variation in muscle fiber size. These myopathic changes, consistent with carnitine deficiency, may be amenable to therapy with L-carnitine replacement.

### 1197 RESPONSE OF VITAMIN D METABOLITES TO CHRONIC SUBERYTHEMAL ULTRAVIOLET B (SE UVB) EXPOSURE IN BLACKS VS WHITES. William F Brazerol, Andrew J McPhee, Stephen A Estes and Reginald C Tsang. University of Cincinnati, Department of Pediatrics and Dermatology, Cincinnati, Ohio.

D deficiency rickets has been reported mainly in black infants, and we have reported lower serum 25-hydroxyvitamin D (25-OHD) in black vs white infants. We hypothesized that race dependent differences in the response of D metabolites to chronic SE UVB may explain these observations. Prior to infant studies, we determined the responses of serum 25OHD, 24,25-dihydroxyvitamin D ( $24,25(\text{OH})_2\text{D}$ ) and 1,25-dihydroxyvitamin D ( $1,25(\text{OH})_2\text{D}$ ) to total body SE UVB given twice weekly for 6 weeks in 13 whites (W) and 7 blacks (B) age 20-35 yrs. Results as mean  $\pm$  SEM; \* $p < 0.001$  vs baseline;  $\dagger p < 0.05$  blacks vs whites; t-test.

Results:		Baseline	Final	Delta
25OHD	W	27.3 $\pm$ 1.4	53.0 $\pm$ 2.7*	25.7 $\pm$ 2.2
	B	11.8 $\pm$ 2.0†	40.7 $\pm$ 4.3*†	28.9 $\pm$ 3.0
1,25(OH) $_2$ D	W	46.9 $\pm$ 5.6	52.0 $\pm$ 5.6	5.3 $\pm$ 4.7
	B	50.4 $\pm$ 7.1	61.3 $\pm$ 3.7	10.9 $\pm$ 3.6
24,25(OH) $_2$ D	W	2.8 $\pm$ 0.4	8.0 $\pm$ 1.0*	5.5 $\pm$ 0.8
	B	0.95 $\pm$ 0.2†	4.3 $\pm$ 0.7*†	3.6 $\pm$ 0.6

25OHD and  $24,25(\text{OH})_2\text{D}$  are lower in blacks vs whites; the increases in 25OHD and  $24,25(\text{OH})_2\text{D}$  are independent of baseline values or race.  $1,25(\text{OH})_2\text{D}$  is similar in both groups and does not change during the study. Thus, race dependent differences in the response of D metabolites to SE UVB do not explain reported differences in D metabolite levels. We speculate that other factors such as duration or extent (surface area) of natural UVB exposure may explain the reported racial differences in D metabolites.

### 1198 ENDOGENOUS GLUCAGON FAILS TO INDUCE HEPATIC PHOSPHOENOLPYRUVATE CARBOXYKINASE (PEPCK) IN NEWBORN GROWTH RETARDED RATS. Mary E. Bussey, Edward S. Ogata, Sandra Finley, Andrew LaBarbera, Northwestern University Medical School, Depts of Pediatrics, OB/Gyn, Physiology, Chicago, IL

Glucagon is a critical hormone for glucose homeostasis in the neonate since it stimulates glycogenolysis and induces gluconeogenic enzymes following birth. To determine its role in the development of hypoglycemia in the growth retarded neonate, we characterized glucoregulation in rat pups growth retarded by maternal bilateral uterine artery ligation (L) and in pups of sham (S) and nonoperated (N) mothers. Birthweight differed significantly (L  $4.11 \pm .05$ ; S  $4.76 \pm .04$ ; N  $5.68 \pm .03$  g;  $p < .01$ ). L pups had significantly lower glucose concentrations at birth, 20 and 240 min, but had normal values at 60 and 120 min. Hepatic glycogen was significantly diminished in L pups. Glucagon in L pups increased significantly at 20 and 60 min (60 min: L  $641 \pm 106$ ; S  $217 \pm 31$ ; N  $318 \pm 28$  pg/ml;  $p < .01$ ) while insulin decreased equivalently in all groups. PEPCK activity increased in S and N but not L pups (240 min: L  $.166 \pm .03$ ; S  $.392 \pm .03$ ; N  $.400 \pm .022$   $\mu$ moles PEP/g liver/min;  $p < .01$ ). Pharmacologic doses of glucagon at birth (plasma conc: 76 to  $143 \times 10^3$  pg/ml) accelerated PEPCK induction and prevented hypoglycemia. By 120 min, L had PEPCK equivalent to S and N pups. Glucagon did not result in supranormal PEPCK in S and N. L pups developed biphasic hypoglycemia because of limited glycogen and delayed PEPCK induction. This delay results from an inadequate though increased glucagon release at birth or relative insensitivity to available endogenous glucagon.

### 1199 TRANSEPIDERMAL EVAPORATIVE WATER LOSS OF PREMATURE INFANTS: EFFECTS OF SKIN COVER WITH PARAFFIN OR A TRANSPARENT ADHESIVE POLYURETHANE FILM. Sergio A. Bustamante and Ann Fiello, University of Arizona Health Sciences Center, Department of Pediatrics, Tucson, AZ

Transepidermal evaporative water loss (TEWL) of premature infants is a significant problem affecting temperature regulation and fluid balance. High relative humidity and covers of various types have been used to reduce TEWL. Using a recently developed evaporimeter we measured TEWL in premature infants simultaneously treated with high humidity, a paraffin ointment (PAR) or a transparent adhesive polyurethane film (TAP). The ten subjects were included in the study after parental consent, had a mean birth weight of 1652.50 gm ( $\pm 89.73$ ; SEM) and gestation of 33.6 weeks ( $\pm 0.5$ ; SEM), were cared for in incubators with servo-control of the temperature and entered the study at a mean age of 3.2 days ( $\pm 0.9$ ; SEM). The relative humidity of the environment at the site of TEWL measures was 65.77% ( $\pm 4.17$ ; SEM). Each infant had one leg covered with PAR (70% solid and 30% liquid paraffin); the other leg was covered with TAP and the buttock area served as the control surface. TEWL measures were made once a day for four consecutive days with minimal disturbance of the subject. Each set of measures was combined to a mean TEWL per site per subject and then analyzed for statistical differences. The mean TEWL of the control was 3.78 gm of water per  $\text{M}^2$  per hour ( $\pm 0.30$ ; SEM), for the TAP group was 1.90 ( $\pm 0.26$ ) and for the PAR group 3.03 ( $\pm 0.28$ ). TAP is significantly better than PAR ( $P < 0.01$ ) and high relative humidity alone ( $P < 0.01$ ) to reduce TEWL.

### 1200 MANIFESTATIONS OF 1,25-HYDROXYVITAMIN D RECEPTORS WITH ABNORMALLY LOW HORMONE AFFINITY: COMPARISON OF TWO KINDREDS. S. Castells, M.A. Fusi, L. Finberg, F. Greig, S. Yasumura, U.A. Liberman and S. Marx, SUNY Downstate Med. Ctr., Depts. of Ped., Phys., Brooklyn, and NIH, Bethesda, MD

We studied two kindreds (A and B) with hereditary resistance to  $1,25(\text{OH})_2\text{D}$ . Clinical and biochemical features included severe rickets, muscle weakness, inability to stand, growth retardation, hypocalcemia, elevated serum PTH, normal  $25(\text{OH})_2\text{D}$ , low plasma osteocalcin and extremely high serum levels of  $1,25(\text{OH})_2\text{D}$ . One dead brother in kindred B had rickets. Both children were treated with  $1,25(\text{OH})_2\text{D}_3$  at 10 mcg  $\text{P}_4\text{O}$  twice daily (5mcg/ml RO-21-5535 Hoffman-LaRoche Lab.) and had good improvement with megadoses of  $1,25(\text{OH})_2\text{D}$  without toxicity. There were features suggesting more severe disease in kindred A versus B. Partial alopecia was present only in the proband of A. Serum levels of  $1,25(\text{OH})_2\text{D}$  associated with normalization of serum Ca were higher in A ( $>4,000$  pg/ml vs 468 pg/ml). Soluble extracts from cultured dermal fibroblasts revealed that interactions with  $1,25(\text{OH})_2\text{D}$  were more abnormal in kindred A than B. The Kd for hormone binding was 2.7 vs 2.0 nM (nl  $0.13 \pm 0.02$ ) and capacity for binding was 19 vs 30 femtomoles/mg protein (nl  $32 \pm 2$ ). The  $24(\text{OH})_2\text{D}$  24-hydroxylase response to a high concentration of  $1,25(\text{OH})_2\text{D}_3$  was undetectable in A vs 0.5 picomoles  $\times 10^6$  cells/30m. in B (nl  $8.2 \pm 1.5$ ). These are the only two known kindreds with a hereditary resistance to  $1,25(\text{OH})_2\text{D}$  associated with low hormone affinity of the receptors. Our results revealed a close relationship between severity of the disease *in vivo* and indices of  $1,25(\text{OH})_2\text{D}_3$  interaction with cells *in vitro*.