223

GLYCOHEMOGLOBIN (Hb A_{1c}): CORRELATION WITH MATERNAL BLOOD GLUCOSE CONTROL IN PREGNANCY. John A. Widness, Herbert C. Schwartz, Diana Thompson, Charles B. Kahn, William Oh and Robert Schwartz; Brown and Stanford Universities, Depts. of Pediatrics and Medicine, Providence, R.I.

Hemoglobin A_{1c} (Hb A_{1c}), the glycosylated form (B-chain) of Hb A, normally comprises <6% of total hemoglobin, but has been found by us previously in third trimester diabetic pregnancy to be elevated (7-10%) and to correlate with infant birth weight. In contrast, non-pregnant uncontrolled diabetics have glycohemoglobin levels which may be 8-15% and may represent the integrated mean blood glucose level over the previous weeks and months. Since fetal size in infants of diabetic mothers has been related to maternal third trimester blood glucose control, we examined the relationship between third trimester maternal Hb A_{1c} and maternal blood glucose control. Twelve diabetic women without evidence of vascular disease and with singleton births had Hb A_{1c} levels determined in their third trimester using Amberlite ion exchange chromatography. Mean random blood glucose values (n=5-32) for each subject were determined for the twelve week period prior to Hb A_{1c} measurement. Hb A_{1c} correlated significantly with mean random blood glucose ($r=0.84$, $p<0.01$) as well as birth weight corrected for gestational age ($r=0.78$, $p<0.01$). In eight of these same women who required insulin, Hb A_{1c} was determined serially 5-8 months postpartum. Seven of eight had higher Hb A_{1c} levels postpartum (6.0 ± 0.5 vs 8.4 ± 0.6 , $M\pm SEM$) at a time when glucose management was not accomplished. We speculate that lower levels of Hb A_{1c} later in diabetic pregnancy are due to better blood glucose control during this period.

226

METHYXANTHINES CAUSE A MARKED REDUCTION IN CHOLESTEROL SYNTHESIS IN CULTURED GLIAL CELLS.

Walter C. Allan and Joseph J. Volpe, Wash. Univ. Sch. Med., St. Louis Children's Hospital, Dept. Ped., St. Louis. Methylxanthines, such as theophylline, aminophylline and caffeine, are used extensively in the treatment of apnea in the neonatal period, a time of active membrane proliferation and myelination in the human brain. C-6 glial cells in culture are good models of the glia found in human brain during this developmental phase. Because cholesterol is a critical constituent of neural membranes, including myelin, we studied the effect of methylxanthines on biosynthesis of this lipid in cultured C-6 glial cells. Exposure of the cells to theophylline, aminophylline, and caffeine for just 24 hours in a concentration of 1×10^{-3} M resulted in marked reductions of cholesterol synthesis (from [¹⁴C] acetate), i.e. 29, 8 and 37% respectively of control values. Cell growth was not significantly affected by the drugs. Lower concentrations produced inhibitory effects after longer exposure times, e.g. theophylline, 5×10^{-4} M, caused a 50% reduction in cholesterol synthesis after 72 hours. To determine whether the methylxanthines cause an alteration in the critical rate-limiting enzyme, HMG-CoA reductase, we assayed this enzyme in treated and untreated C-6 glial cells. A marked decrease in reductase activity accompanied the decrease in cholesterol synthesis. The mechanism of this effect is currently under investigation. These data raise the possibility that methylxanthines have a deleterious effect on the development of the human brain.

224

EFFECT OF CARNITINE ON KETONE BODY PRODUCTION IN HUMAN NEWBORNS. Paul B. Wieser, Maria Buch, Milan Novak, Univ. of Miami School of Medicine, Dept. of Pediatrics, Miami, FL.

The importance of carnitine as an intermediary in fatty acid oxidation in newborn mammals is well recognized. In newborn infants who are maintained on diets which contain no carnitine (i.e. soy protein based formulas) there is a significant decrease in the plasma levels of carnitine and acetylcarnitine compared to plasma levels in infants who are receiving diets which contain carnitine (human breast milk and cow's milk based formulas). The plasma concentration of β -hydroxybutyrate is significantly lower in the group of infants maintained on a carnitine free diet; moreover plasma β -hydroxybutyrate increases logarithmically with increasing plasma carnitine. There is also a direct correlation between the plasma concentration of acetylcarnitine and β -hydroxybutyrate.

These results suggest that the absence of dietary carnitine during the newborn period results in a less than optimal concentration of carnitine in liver, indicated by decreased ketone body production, in infants whose plasma concentration of carnitine and acetylcarnitine is low. It is not clear at present whether carnitine is increasing ketone body production by stimulating fatty acid oxidation and producing excess acetyl Co A or if carnitine, after conversion to acetylcarnitine, can participate directly in ketone body production.

Supported by NIH grant No. HD04946.

227

THE EFFECT OF PHOTOTHERAPY ON SERUM IMMUNOREACTIVE PROSTAGLANDIN A LEVELS. Charles E. Aplin, Ben H. Brouhard, Robert J. Cunningham, C. Joan Richardson,

University of Texas Medical Branch, Department of Pediatrics, Galveston, Texas. (Spon. by Luther B. Travis).

Phototherapy (PT) accelerates photo-oxidation and breakdown of unsaturated fatty acids (UFA) in premature infants. Since UFA serve as precursors for prostaglandins (PG), PT may effect PG metabolism. To assess this serum immunoreactive prostaglandin A (iPG-A) levels were measured in 9 prematures prior to PT, after 24 and 48 hours of PT, and 24 hours after PT was discontinued. Three infants had a patent ductus arteriosus (PDA).

Results:

		Serum iPG-A (ng/ml; mean $\pm$ SEM)					
		Weight (gm)	Gest. (wks)	Pre PT	24 PT	48 PT	Post PT
PDA	3	1357 $\pm$ 313	31 $\pm$ 2	7.1 $\pm$ 2.5	2.2 $\pm$.9	1.2 $\pm$.8	0.8 $\pm$ 0.2
No PDA	6	1953 $\pm$ 135	33 $\pm$.6	0.6 $\pm$ 0.2	0.3 $\pm$ 0.2	0.2 $\pm$ 0.1	1.1 $\pm$ 0.4

Serum iPG-A levels decreased during PT. Pre-PT iPG-A levels were significantly higher in preterm infants with a PDA compared to infants without a PDA ($P<0.02$). However, after 48 hours of PT the levels were not significantly different. The data suggest that phototherapy in premature infants may effect iPG-A levels. This effect of PT could be important in clinical situations where manipulation of PG synthesis is desirable.

DEVELOPMENTAL PHARMACOLOGY

225

FUROSEMIDE POTENTIATED GENTAMICIN NEPHROTOXICITY. R. D. Adelman, G. Conzelman, W. Spangler, G. Ishizaki (Spon. by E. Gold). Schools of Medicine and Veterinary Medicine, University of California, Davis.

The effect of furosemide (F) on gentamicin (GN) nephrotoxicity was examined in a dog model.

GN 10 mg/kg and F 2 mg/kg were given IM every 8 hours for 9 days. Elevation of BUN and serum creatinine values was earlier and more marked than in dogs given only GN. Serial percutaneous renal biopsies showed earlier and more severe renal injury in GN+F dogs. Increased activities of the urinary enzymes muramidase (MUR), B-glucuronidase (BG) and N-acetyl-glucosaminidase (NAG) were early signs of biopsy confirmed renal injury.

DAY	MUR [§]	BG	NAG	CREAT ^s	BUN
Contr.	5	21	534	0.75	16
Contr. (F)	3	31	780	0.81	22
4 (GN)	2	49**	828*	0.85	19
4 (GN+F)	8	63**	1066	1.11	24
6 (GN)	75**	52**	951**	0.91*	20
6 (GN+F)	186**	108**	1062	1.62**	50**
8 (GN)	172**	111**	1765**	1.15**	24*
8 (GN+F)	1766**	231**	3766**	4.75**	181**

Furosemide appears to potentiate gentamicin nephrotoxicity, perhaps in relation to volume depletion. Elevated urinary enzyme activities provide an early clue to the onset of renal injury.

[§]Mean enzyme activity $\pm$ SEM expressed as U/mg of urinary creatinine. * $p<0.05$, ** $p<0.01$ [compared to control or control (F) values].

228

FETAL HEMODYNAMIC AND BRAIN FUNCTION (EEG) EFFECTS OF DIAZOXIDE (D) INFUSION INTO THE OVINE FETUS. Jahangir Ayromloo (Spon. by P.

Lipsitz), SUNY Med. Sch. at Stony Brook, Long Island Jewish-Hillside Med. Ctr., Dept. Ob-Gyn, New Hyde Park, N.Y.

D has been used to stop premature labor. D crosses the placenta. Bolus intravenous D ($8.4\text{ mg/kg} \pm 0.57\text{ SE}$) was given near term to 6 fetal lambs during an acute experiment. Post-infusion changes $\pm$ SE of baseline fetal carotid (FC) pH, pO_2 , O_2 saturation ($\text{O}_2\%$), pCO_2 , blood pressure (FBP) are presented in this table:

Time	0	5 Min.	15 Min.	30 Min.
pH	7.33 $\pm$ 0.038	7.30 $\pm$ 0.051	7.28 $\pm$ 0.44*	7.27 $\pm$ 0.046*
pO ₂	19.3 $\pm$ 0.92	16.4 $\pm$ 1.61*	19.4 $\pm$ 1.20	19.7 $\pm$ 1.83
O ₂ %	53.9 $\pm$ 8.90	41.0 $\pm$ 8.48*	50.9 $\pm$ 8.44	47.7 $\pm$ 9.12
pCO ₂	28.5 $\pm$ 2.29	28.8 $\pm$ 3.02	30.8 $\pm$ 3.27	34.6 $\pm$ 2.56
FBP	38.5 $\pm$ 4.08	34.9 $\pm$ 4.69	36.2 $\pm$ 3.25	48.7 $\pm$ 5.24

* $p<0.05$

Isoelectric EEG occurred within 5 min. post D infusion in 3 experiments. Conclusion: D infusion into the fetus may cause hypoxia, acidosis and isoelectric EEG.