

199

DEVELOPMENT OF GLYCOGEN AND PHOSPHOLIPID METABOLISM IN FETAL AND NEWBORN RAT LUNG. William M. Maniscalco, Christine M. Wilson, Ian Gross, Joseph B. Warshaw.

Yale University School of Medicine, Department of Pediatrics, New Haven, Connecticut

Fetal rat lung glycogen content decreases as phosphatidylcholine (PC) content increases during lung maturation. We have investigated glycogen and PC metabolism in fetal and newborn rat lung. Lung glycogen concentration was maximal on day 20 of gestation (term = 22 days) and then fell to low levels by 1 day of age. Glycogen synthetase I (the active form in adult muscle) activity increased two fold from day 18 of gestation to day 21. Glycogen synthetase D activity was 6-7 times greater than synthetase I, increased two fold from day 19 to day 22 and fell by 50% after birth. Glycogen phosphorylase a (the active form) activity increased two fold from day 19 to day 22 and fell after birth. Phosphorylase b activity remained low throughout the study period. The PC content of the lungs increased by 60% from day 19 to day 1 of life. Seventy-five percent of this increase was due to an increase in the disaturated form. The rate of incorporation of ^3H -choline into PC increased 10 fold from day 19 to day 1 of age. During this time, the fraction of labelled PC that was disaturated increased from 35% to 43%. This temporal relationship between decreasing lung glycogen content and increasing lung PC content and synthesis suggests that carbohydrate derived from glycogenolysis in fetal rat lung may provide substrate or energy for PC synthesis.

202

ONTOGENY OF CANINE CARDIAC BETA-ADRENERGIC RECEPTORS. Stephen Montgomery, Seymour Hepner, and Pedro Jose.

Georgetown Univ. Sch. of Med., Georgetown Univ. Hosp., Dept. of Peds., Wash., D. C.

Age differences in cardiac chronotropic and inotropic responsiveness to adrenergic agonists and antagonists have been reported. These developmental differences were evaluated at the molecular level by characterizing myocardial beta adrenergic receptors in puppies (1-3 wks old) and adult mongrel dogs.

Partially purified cardiac plasma membranes (10,000-30,000xg) were obtained by differential centrifugation techniques. Beta adrenergic receptors were identified using the beta adrenergic antagonist ^3H -dihydroalprenolol according to the method of Alexander et al (Proc Nat Acad Sci. 72:1546, 1975). Saturable binding sites were quantified using increasing concentrations of the labelled ligand in the presence of 10^{-5}M propranolol. Specific binding was 65% in puppies (n=20) and 80% in adult dogs (n=6). Scatchard plot analyses showed a greater number of receptors ($p < 0.05$) in the adult than in puppies: 0.3275 ± 0.0143 vs 0.2151 ± 0.0105 pM/mg protein. Dissociation constant for the puppies was greater ($p = 0.05$) than adults: 10.7112 ± 1.25 vs 4.0224 ± 0.6746 .

These data suggest that the maturation of adrenergic responsiveness of the myocardium may be due to developmental changes in beta adrenergic receptor affinity and number.

200

PREDICTING HUMAN FETAL MALNUTRITION (FM). Jack Metcalf, Paul Costiloe, Warren Crosby, Harold Sandstead, Philip McClain, Larry Bentle, Sesh Dutta, MMFD Team. U. Okla. Health Sci. Ctr. Okla., Human Nutrit. Lab (Grand Forks, ND) and Protein Nutrit. Lab (Beltsville, MD) ARS, USDA.

We hypothesize that during pregnancy maternal nutrition regulates metabolism of all rapidly replicating cells, including maternal leukocytes, as well as those of fetus & placenta. Fetal malnutrition complicates about 6-8% of all pregnancies in the U.S.A. FM babies are at high risk for congenital anomalies & impaired postnatal physical & mental development. It is often unrecognized when birth wt. < 2500 g. @ 37+ weeks gestation, is used to identify FM babies, since babies are too small if their observed size (wt., length, head circumference, arm & thigh muscle area, & fat folds, etc.) is more than one SD (approx. 450 g.) below their expected size when adjusted for sex, gestational age and maternal age, ht., pre-preg. wt., race and parity. Currently, prospective data have been obtained from 584 mother-baby pairs. 294 had no detected complications during pregnancy and their data was used to adjust baby size. Operationally, maternal dietary intake, plasma levels of 11 nutrients & 19 amino acids, hair root protein & DNA, & metabolism of maternal leukocytes as an indicator of fetal cell metabolism, all measured only once at mid-pregnancy, were used as independent variables to predict deviations from expected baby size. Significant multiple correlation coefficients were found for principal components relating maternal mid-pregnancy nutrient, amino acids, & leukocyte measures to adjusted birth size of the baby. These data support our hypothesis. The prediction equations require further refinement, but offer promise to predict fetal growth & identify mothers at mid-pregnancy who are carrying malnourished fetuses. Supported by USPHS, NICHD-06915

We hypothesize that during pregnancy maternal nutrition regulates metabolism of all rapidly replicating cells, including maternal leukocytes, as well as those of fetus & placenta. Fetal malnutrition complicates about 6-8% of all pregnancies in the U.S.A. FM babies are at high risk for congenital anomalies & impaired postnatal physical & mental development. It is often unrecognized when birth wt. < 2500 g. @ 37+ weeks gestation, is used to identify FM babies, since babies are too small if their observed size (wt., length, head circumference, arm & thigh muscle area, & fat folds, etc.) is more than one SD (approx. 450 g.) below their expected size when adjusted for sex, gestational age and maternal age, ht., pre-preg. wt., race and parity. Currently, prospective data have been obtained from 584 mother-baby pairs. 294 had no detected complications during pregnancy and their data was used to adjust baby size. Operationally, maternal dietary intake, plasma levels of 11 nutrients & 19 amino acids, hair root protein & DNA, & metabolism of maternal leukocytes as an indicator of fetal cell metabolism, all measured only once at mid-pregnancy, were used as independent variables to predict deviations from expected baby size. Significant multiple correlation coefficients were found for principal components relating maternal mid-pregnancy nutrient, amino acids, & leukocyte measures to adjusted birth size of the baby. These data support our hypothesis. The prediction equations require further refinement, but offer promise to predict fetal growth & identify mothers at mid-pregnancy who are carrying malnourished fetuses. Supported by USPHS, NICHD-06915

203

POLYAMINE AND NUCLEIC ACID ALTERATIONS FOLLOWING TERATOGENIC TREATMENT WITH DIPHENYLHYDANTOIN. M.L. Netzloff, A.D. Garnica. (Spon. by A.L. Rosenbloom), U. Florida College of Medicine, Dept. Pediatrics, Gainesville.

Polyamines are closely bound to nucleic acids; their levels correlate with nucleic acid synthesis and may decrease during interference with such synthesis. We have previously reported decreases in embryonic polyamines per mg protein after exposure to diphenylhydantoin (DPH) in teratogenic doses. We now report alterations in nucleic acid levels following identical treatment. Primigravid Swiss-Webster mice were injected intraperitoneally on day 9 with either 88 mg DPH/kg body weight or vehicle and embryos were obtained surgically on day 11 (DPH or control n=13). DNA content was determined spectrophotometrically and the polyamines spermidine, spermine, and putrescine were quantitated on a Durrum D-500 amino acid analyzer. There was a 40% decrease in DNA content in the treated embryos (99.4 vs 164 ug DNA). The protein contents decreased 30% compared with controls (2.38 vs 3.38 mg). All experimental polyamines per mg DNA were significantly greater than their controls ($P < 0.01$) (putrescine: 0.155 ± 0.034 (std. dev.) vs 0.0834 ± 0.009 ; spermidine: 0.379 ± 0.066 vs 0.264 ± 0.028 ; spermine: 0.177 ± 0.034 vs 0.136 ± 0.026 nM/ug DNA). The DPH-induced polyamine changes are not proportionate to the DNA alterations and thus do not simply reflect a block in DNA synthesis.

201

THE RELATIONSHIP OF AMNIOTIC FLUID DEHYDRO-ISOANDROSTERONE SULFATE (DS) AND CORTISOL (F) CONCENTRATIONS WITH LECITHIN TO SPHINGO-

MYELIN (L/S) RATIOS DURING HUMAN GESTATION. Leon Milewich, John M. Johnston, Debra J. Bradfield, William N.P. Herbert, Paul C. MacDonald and Juan M. Jimenez. Univ. Texas Southwestern Med. Sch., Dept. Ob-Gyn, Dallas, Texas. (Spon. by Charles Rosenfeld).

We have measured L/S ratios, together with the concentrations of F and DS of 414 amniotic fluid specimens obtained from 13 to 44 weeks gestation. We found that the L/S ratios begin to increase after 33 weeks gestation, from mean values of 0.7 ± 0.2 (\pm SE) at 33 weeks to 1.8 ± 0.3 at 34 weeks and 3.5 ± 0.7 at 35 weeks. There are no significant differences in concentrations of amniotic fluid F from 31-32 weeks up to 35 weeks. F concentrations rise thereafter from 51 ± 6.3 ng/ml at 35 weeks to 63 ± 4.5 ng/ml at 36 weeks and 67.5 ± 6.3 ng/ml at 37 weeks. DS concentrations in amniotic fluid rise slowly from 31-32 weeks (80 ± 13 ng/ml) to the 35th week (110 ± 7.8 ng/ml) and this rise continues to term. While others have shown that the L/S ratios in amniotic fluid correlate well with fetal lung maturation, this does not appear to be the case with cortisol, since cortisol concentrations increase following the increases of L/S ratios. However, DS concentrations in amniotic fluid do begin to increase before the rise in the L/S ratio, likely reflecting increased availability of fetal placental estrogen precursor. Augmented estrogen production could serve a role in increasing fetal lung surfactant synthesis, perhaps by leading to increased fetal pituitary prolactin secretion.

204

INSULIN BINDING STUDIES IN NORMAL INFANTS (NI) AND INFANTS OF DIABETIC MOTHERS (IDM). Naomi D. Neufeld, Solomon A. Kaplan and Barbara M. Lippe. UCLA School of Medicine, Department of Pediatrics, Los Angeles.

Insulin excess has been implicated in the greater perinatal morbidity and mortality in IDM. Since insulin acts by binding to cell surface receptors, we studied the receptors on cord blood monocytes of 22 NI and 8 IDM delivered by elective C-section at 36-38 wks. gestation. IDM had more receptor sites per monocyte (105,000) than NI (38,000) and 12 normal adults (25,000) studied similarly. The higher number of receptors in IDM occurred in the face of higher concentrations of insulin in their cord blood than in NI. Monocytes from both NI and IDM showed greater affinity for insulin than those from adults, (4.63 and 4.55 vs. $2.35 \times 10^8 \text{ M}^{-1}$ $p < 0.025$). In NI of similar gestational age, a significant correlation was found between birthweight and insulin binding. Insulin binding to liver plasma membranes of fetal rats increased progressively from 14 d gestation through birth. At birth the maximum binding capacity was significantly greater per 100ug protein (25ng insulin) than in adult rat membranes, (17ng insulin, $p < 0.025$). Scatchard analysis also showed that binding affinity constants were markedly greater for term fetuses than adults ($K_e = 3.94 \times 10^8$ vs. $2.85 \times 10^8 \text{ M}^{-1}$). Thus, in contrast to down-regulation of receptor number reported in adult hyperinsulinemia, IDM have an increase in receptor number which may be an exaggeration of the developmental process observed in normal fetuses. Greater binding of insulin to tissue of IDM may therefore expose these infants to greater hazards from the effects of insulin.