DEVELOPMENT OF TRANSSYNAPTIC REGULATION OF ADRENAL TRANSMITTERS E.F. La Gamma & J.E. Adler, Pediatrics & Neurobiology, SUNY at Stony Brook, and Neurology, Cornell Medical Center, New York.

●266

Transsynaptic activity differentially regulates biosynthesis of sympathoadrenal catecholamines (CA) and co-localized opiate peptides in the rat (La Gamma, et al PNAS 82: 8252, 1985). We determined whether similar mechanisms were operative during development. Adrenal leu-enkephalin (LEU), first detected at E0.75, increased 20 fold during maturation from birth to adulthood while medullary weight increased only 10 fold. Since medullary cells do not divide after birth, this represents a specific maturational increase in LEU content per chromaffin cell. In adult medullae, decreasing transsynaptic activity through adrenal denervation or explantation results in a 30 to 50 fold increase in LEU (La Gamma, et al Science 224:1102, 1984). In contrast, LEU levels in denervated or explanted medullae from neonatal rats (<10 days) do not. Prolonged denervation (5 to 21 days) blocked even the normal maturational increase in LEU. Moreover, increased activity through nicotine treatment also failed to affect LEU levels in neonates. Specific deficits in nicotinic receptor transduction mechanisms or immaturity of opiate biosynthesis pathways may account for these observations. Therefore, like CA pathways, adrenal opiate peptides require presynaptic regulatory signals to achieve normal development. Defining transmitter ontogeny and identifying essential cellular processes will help elucidate mechanisms of sympathoadrenal exhaustion or dysfunction and thus promote the development of innovative therapy for syndromes of autonomic dysfunction in neonates. Supported in part by the March of Dimes Foundation.

DELAYED FETAL LUNG MATURATION IN THE DIABETIC MOUSE. Stewart Lawrence and Heber C. Nielsen, Southwestern Medical School, Dept. of Pediatrics, Dallas, TX.

†267

Mouse fetuses from the genetic diabetic mouse are macrosomic with increased body, lung and placenta weights and have abnormal carbohydrate metabolism with increased liver and placenta glycogen content. We studied the effect of increased glucose availability and utilization on lung growth and maturation in these fetuses at 18 days gestation (term=19). Phospholipid synthesis in lung slices was measured as ^{3}H-choline incorporation into phosphatidylcholine (PC) and disaturated PC (SPC) and ^{14}C-glycerol incorporation into phosphatidylglycerol (PG) and phosphatidylinositol (PI). The diabetic fetuses had significantly higher SPC synthesis than controls (881±65 vs 520±33 CPM/mg prot; mean±SE; p<.001) but significantly lower PG synthesis (212±26 vs 327±35 CPM/mg prot; mean±SE; p<.02), with a lower ^{14}C-PG/^{14}C-PI ratio (1.81±.18 vs 3.17±.14; mean±SE; p<.001). Diabetic fetal lungs were morphologically less mature than controls, as shown by a significantly decreased air space density (.27±.01 vs .43±.02; mean±SE; p<.001) and alveolar epithelial cell/total tissue ratio (.54±.02 vs .66±.03; mean±SE; p<.01). Increased SPC synthesis in diabetic fetal lung may reflect the enhanced lung growth resulting in macrosomia. Lung maturation may be represented more specifically by PG synthesis, the PG/PI ratio, and morphologic indices, all of which were decreased in diabetic fetuses. Thus enhanced growth appears to coincide with delayed maturation. Further studies with this model of genetic diabetes will help clarify the mechanisms causing enhanced growth and delayed lung maturation in the infant of a diabetic mother.

ACCELERATED ORGAN MATURATION IS ASSOCIATED WITH INCREASED BINDING OF EPIDERMAL GROWTH FACTOR (EGF) IN IUGR PREGNANCIES. Stewart Lawrence, Janice F. Sissom, Wendy K. Stenzel, and Joseph B. Warshaw. Dept. of Pediatrics, Southwestern Med. Sch., Dallas, TX.

▲268

Delayed maturation of lung and placenta of fetuses from streptozotocin-induced diabetic rats is associated with decreased binding of EGF to membranes prepared from these organs. In order to examine the hypothesis that substrate supply is important in mediating these alterations, we induced intrauterine growth retardation (IUGR) via unilateral ligation of the inferior uterine artery on day 17 of gestation (term=22). There was a significant reduction in mean weights of body, placenta and lung (29%, 14% and 38% respectively) in fetuses on day 20, as compared to controls from the contralateral uterine horn. Caloric restriction in this model was reflected by significantly decreased glycogen content of IUGR placentas (29±2 vs. 35±2 µg/mg protein; mean±SE; p<.05) and lungs (332±53 vs. 440±27 µg/mg protein; mean±SE; p<.05). The lungs of IUGR fetuses were morphologically more mature with thinner alveolar walls and an increased ratio of air space density to total tissue (.45±.03 vs. .27±.02; mean±SE; p<.005), but there was no significant difference in whole lung phospholipid synthesis. Specific binding of EGF to placenta membrane was significantly increased in IUGR fetuses (23.4±1.7 vs. 18.1±1.6 % binding/mg protein; mean±SE; p<.05) and correlated with the extent of placental growth restriction (r=.601; p<.01). These changes, which are the opposite of those observed in fetuses of diabetic rats, suggest that nutrient availability influences the timing of organ maturation late in gestation, and its effect may be mediated through tissue binding of endogenous EGF.

LACTATE(L) AND FRUCTOSE(F) ARE GLYCOGENIC PRECURSORS IN THE CHRONICALLY CATHETERIZED BABOON FETUS Lynne L. Levitsky, John B. Paton, and David E. Fisher, Pritzker Sch. Med., U. Chicago and Michael Reese Med. Ctr. Depts. Pediat., Chicago

▲269

In order to assess the contribution of the direct [phosphorylation(P) of glucose] vs indirect [P of other precursors) pathway of glycogenesis in the fetus(fet), ten baboon fet of 140 d gestation were studied after placement of femoral artery (FA) and umbilical vein(UV) catheters. On day 4 post surgery, after a 24h fast, maternal(mat) baboons were sedated and mat plasma glucose(G) was raised to 68±3 mg/dl with 10%G to mat vein. A primed dose of 50 uc/h U-14C L and 2-3H G (n=5), or U-14C F and 3-3H G(n=5) was infused to steady state into the UV over 3h. Six FA samples were obtained 90-180 min, the fet was sacrificed under mat-fet general anesthesia, and kidney and liver removed for determination of glycogen (gly) and 14C, 3H gly enrichment. Fetal blood 14C G derived from L SA was 4.0±.5, 14C G from F SA was 11.0±1.5, 2-3H G SA was 42.0±2.5, and 3-3H G SA was 35.0±5.(uc/mg(10^3). Organ gly SA was calculated as uc/mg(10^3):

Organ	14C(L)	14C(F)	2-3HG	3-3HG
Liver	3.07±2.60	23.63±10.52	.78±.68	4.25±2.0
Kidney	1.70±.43	1.76±.08	.08±.01	.83±.17

SA organ gly/SA G reflects the fraction of gly derived from label. 14C SA kidney gly/SA G was greater than 2-3H or 3-3H ratio for F and L fet(p<.004). 14C SA liver gly/SA G was greater for F vs 2-3H, 3-3H(p<.002, p<.05) and L vs 2-3H(p<.002), but similar for L fet vs 3-3H. This is more than can be explained by intraorgan futile cycling. The indirect pathway may be an important route of glycogenesis in gluconeogenic organs of the fetus.

ACIDEMIA POTENTIATES THE PLASMA CATHECHOLAMINE(CA) RESPONSE TO HYPOXEMIA(HYP) IN FETAL SHEEP. **Alan B. Lewis, Mahvash Sadeghi. University of Southern California School of Medicine, Childrens Hospital of Los Angeles, Division of Cardiology, Los Angeles.**

270

Though hyp has been shown to stimulate adrenal medullary CA release and raise plasma CA concentrations, it is unclear whether acidosis influences the magnitude of this response. Eleven chronically catheterized late gestation(0.8) fetal lambs in utero were investigated during a baseline control period and following the onset of umbilical cord constriction-induced hypoxemia (PO2=5-15 torr). The data were segregated based upon the fall in pH. Plasma CA rose in response to hypoxemia, but were potentiated by the development of acidosis (pH=7.19±.02). Baseline NE(487±113 pg/ml) increased to 1386±127 pg/ml (p<.001) in response to hyp alone but rose to 6726±1289 pg/ml (p<.05) in the presence of hyp+acidosis. Hyp increased plasma E from 99±36 pg/ml to 512±81 pg/ml (p<.001). However, an additional 9-fold increase (p<.05) was noted when hyp was combined with acidosis (E=4311±1449 pg/ml). Thus, acidosis significantly potentiates the magnitude of the plasma CA response to hyp in the late gestation fetus.

PRENATAL HEMATOLOGICAL INDICES DURING GESTATIONAL DEVELOPMENT AS DETERMINED BY PERCUTANEOUS UMBILICAL BLOOD SAMPLING. Abraham Ludomirski, Vinod K. Bhutani, Ronald Librizzi, Ronald Bolognese. Spon. by Lois H. Johnson. Univ of PA Sch of Med, Pennsylvania Hosp, Sec. of Perinatology & Newborn Pediatrics, Phila, PA.

271

Direct access to fetal blood by an ultrasonographically guided needle is now feasible and overcomes the limitations of earlier sampling techniques such as placentocentesis, fetoscopy and scalp sampling. Percutaneous umbilical blood sampling (PUBS) of 92 fetuses were performed for a variety of fetal indications: suspected prenatal hematological diseases, rapid chromosomal evaluation, etc. Of these, 50 fetuses (17 to 37 wks gestation) were deemed normal at birth and postnatal evaluation and were evaluated retrospectively for the hematological indices. Values of hemoglobin (HGB), red blood cells (RBC), mean corpuscular volume (MCV), white blood cells (WBC) and platelet (Plt) counts were correlated to gestational age (GA). Linear regression equations are listed:

HGB $(gm/dl)_3$ = 9.39 + 0.076 (GA); r = 0.51; (p<0.01)
RBC (per mm^3) = 2.52 + 0.067 (GA); r = 0.38; (p<0.01)
MCV (per µm3) = 142.0 - 1.02 (GA); r = 0.65; (p<0.01)

Fetal values indicate a relative neutropenia (WBC: 3.0-6.0 x10^3). Values of both WBC and Plt counts (150-250,000) did not change significantly during gestation. These data define an increase in both HGB and RBC and concommitant decrease in MCV with advancing GA. This study describes and demonstrates the normative changes in hematological indices during fetal development prior to the onset of labor and delivery.