247 THYROIDAL STATUS MODULATES THE INSULIN(I) RECEPTOR (R) CHARACTERISTICS OF THE DEVELOPING BRAIN(B) S.Devaskar, N.Holkamp, N.Marino and U.Devaskar (Spons W.J.Keenan) Dept. of Peds., St. Louis University, St. Louis, MO

I's role via its R in the brain, unlike other organs is unknown. Hypothyroidism(HP) influences fetal(F) lung and liver IR and retards B metabolism. The ontogeny of B IR in plasma membranes(PM) was examined to explore the role of I in rabbit F (30d.) and newborn(N) B (1d,6d). Groups with PTU-induced HP(F and N), N with T_4 corrected HP (ET) and hyperthyroidism(HT) were also studied. Specific ^{125}I-I binding/200µg BPM (IB), IR no.x10^{10}mg prot.$^{-1}$ and affinity (Kex10^{9}=0.91±.08) were determined. (UD=undetectable, p < .01 vs. control (C)).

Age (days)		F(30)		N(1)				N(6)
Groups (n)		C(6)	HP(5)	C(5)	HP(5)	ET(4)	HT(4)	(5)
% IB	X̄±	12.3	13.8	15.7	12.3*	15.0	17.7*	12.1
	SEM	0.6	0.4	0.4	0.4	0.4	0.3	0.7
I.R. No.		175.0	153.0	259.0	143.0*	272.0	476.0*	89.0
		12.0	19.0	24.0	10.0	13.0	10.0	11.0
F-serum free T_4		.19	UD	.38	.09*	.52	1.87*	-
(ng/dl)		.01		.019	.04	.10	.20	
B cholesterol		2.6	2.2	7.0	2.9*	-	-	3.2
(mg/g)		0.2	0.1	1.0	.10			0.2
B Protein		54.0	59.0	46.0	47.5	66.0*	67.0*	39.0
(mg/g)		2.0	2.1	6.6	1.3	1.7	0.7	1.8

Brain DNA did not change, IR no. expressed/DNA revealed similar trends. (Preliminary culture studies revealed specific IB to isolated 1d N neurons). We suggest that the NB IR changes induced by ↑ or ↓ by T4 in part mediate the changes in B metabolism, the fetus being unresponsive.

250 DEVELOPMENTAL ASPECTS OF CYSTINE TRANSPORT IN THE DOG. J.W. FOREMAN, M.S. MEDOW, K. GINKINGER AND S. SEGAL, U. of Penn. School of Med., Children's Hosp of Phila., Dept. of Peds., Phila., PA. 19104

Increased amino acid excretion is a characteristic of developing rat, dog and man. The mechanisms underlying this physiologic aminoaciduria are unclear. We have shown faster cystine entry into isolated renal tubule cells from newborn rats compared to adults, despite impaired in vivo reabsorption. To see if these observations extend to other animals, we examined the fractional reabsorption (FR_c) of cystine in developing dogs and cystine uptake by isolated renal cortical tubule fragments from newborn (NB) and adult dogs. FR_c was 67% of the filtered load in five day old dogs but reached the adult value of 99% by 21 days of life. Isolated renal cortical tubules from NB dogs progressively accumulated label when incubated for 60 min. with a physiologic concentration of cystine (0.025 mM), although this uptake was lower than that observed in adults. Nearly complete conversion of transported labelled cystine to cysteine occurred in the NB and adult as previously noted for rat tubules. Kinetic analysis of uptake indicated two systems for cystine entry in both adult and NB. The affinity constants (Km) for the newborn systems were Km_1 = 0.08 ± 0.01 and Km_2 = 0.33 ± 0.03 mM. The corresponding values for adult were significantly higher - Km_1 = 0.14 ± 0.02 and Km_2 = 0.66 ± 0.09 mM. The maximal uptake rate for each NB system was only 1/3 that of the adult. These data suggest that, in contrast to the rat, the impaired cystine reabsorption by NB dog kidney in vivo is related in part to a slower flux of cystine into the renal tubule cells.

● 248 A NOVEL MODEL OF MATERNAL HYPOAMINOACIDEMIA. Mercedes Domenech, Philip A. Gruppuso, Vincent T. Nishino, John B. Susa and Robert Schwartz. Dept. of Pediatrics, Brown Univ., Providence, RI.

Chronic hyperglucagonemia produces persistent hypoaminoacidemia (HA). Glucagon does not cross the placenta; therefore, the effects of low maternal amino acids on the fetus could be studied. Alzet pumps delivered glucagon (0.25 mg/d) s.c. in 8 rats fed ad lib from d. 14 to 20 of gestation. Ten controls were sham-operated. Blood was obtained prior to implantation, at d. 3, and before delivery for total amino acids (α-amino nitrogen), glucose, and insulin. Four dams (HA-A) had weight gain and caloric intake comparable to controls; the other 4 (HA-B) gained no weight and had 1/3 lower caloric intake. Glucose conc. declined comparably from d. 14 to 20 in all groups. Insulin was unaffected in HA-A, but decreased in HA-B.

TOTAL α-AMINO NITROGEN (mM)

	Control	[HA-A]	Experimental	[HA-B]	P
Maternal d. 0	3.60±0.68 (M±SD)		3.28±0.55		NS
d. 3	3.38±0.35	1.68±0.70		1.53±0.35	.001
d. 6	3.51±0.23	1.45±0.13		1.70±0.20	.001
Fetal	9.77±1.95 (n=29)	8.55±1.03 (12)		8.95±1.35 (9)	NS

Fetal weight on day 20 was 4.01±0.37 g in controls (n=102), 3.90±0.51 in HA-A (45), but 3.05±0.27 in HA-B (48). Fetal glucose and insulin levels were similar as were fetal amino acid levels. The latter resulted in higher feto-maternal ratios in both HA groups (p <0.001). Thus, hypoaminoacidemia in mothers with normal weight gain did not affect fetal weight due to the ability of the conceptus to maintain total amino acid levels.

● 251 PROLONGATION OF TOLERANCE TO PULMONARY O_2 TOXICITY BY CASTRATION OF YOUNG MALE RATS. Lee Frank, Kazuo Neriishi, Pamela Lewis and Rey Sio. Univ. of Miami Sch. of Med., Pulm. Res. Div., Dept. of Medicine, Miami.

Neonatal animals of several species are relatively resistant to pulmonary O_2 toxicity. Young rats progressively lose their O_2 tolerance after age 30 days, which is approximately the time of pubertal sex hormone surges. We therefore castrated male (CAST) and female (OVARX) rats at age 20 days and exposed them to hyperoxia at ages 45 to 80+ days to determine whether endocrine changes are important to age-related loss of O_2 tolerance. Survival results (100% O_2, 72 hrs):

Group	Survival	Serum testosterone(pg/ml)
SHAM(Control)	59/156(38%)	1157±389(11)
CAST	115/166(69%)*	29±21 (11)*
CAST + TESTO**	30/87 (34%)	≥1200 (6)

*p<0.001 compared to other groups; **Testosterone replacement (50mg/kg/week) after castration.

The findings that female castration had no protective effect against hyperoxia (survival at age 55 days: SHAM=14/28 vs. OVARX=16/33), and that TESTO replacement reversed the improved survival seen in CAST male rats at all ages tested, indicate an important role for TESTO in the loss of O_2 tolerance. CAST (but not OVARX) was also associated with altered lung development, including increased lung volume (4.54±.72 vs. 3.76±.29ml/100gms for SHAM controls)(p<0.01) and morphometric evidence of significantly enlarged alveoli. The post-natal role of TESTO in lung development (and tolerance/susceptibility to O_2 toxicity) is a potentially fertile new area for future study.

249 ACUTE METABOLIC ACIDOSIS: EFFECTS ON ARGININE VASOPRESSIN (AVP) RELEASE IN FETAL SHEEP. Daniel J. Faucher, Tom Lowe, Abbot Laptook, John C. Porter and Charles R. Rosenfeld, Univ. Texas Southwestern Med. Sch., Dept. Peds. and OB-Gyn, Dallas, Tx.

Acute asphyxia results in AVP hypersecretion in fetal sheep. Since acidosis, hypoxia, and hypercapnea occur simultaneously with asphyxia, it is unclear which is primarily responsible for AVP release. We have shown that hypoxia has no effect until aortic PO_2 (PaO_2) is <12mmHg, and AVP levels were only 10±3µU/ml (X̄±SE). To further examine the asphyxial components in fetal AVP release, we studied the effects of metabolic acidosis in 8 fetal sheep at 137±1.4 days. Each was infused with .03-.07mEq NH_4Cl/min·kg for 120min while monitoring mean arterial pressure (MAP), heart rate (HR), PaO_2, pHa, and $PaCO_2$, and plasma AVP before, during (20min intervals) and repeatedly after NH_4Cl. MAP, PaO_2, and $PaCO_2$ were unchanged; pHa fell progressively from 7.376±.012 to 6.986±.066* during NH_4Cl, rising to 7.356±.021 by 24h. Plasma AVP rose gradually from 2.85±.23 to 5.26±1.1µU/ml* during NH_4Cl, falling to 2.77±.41 by 4h. After NH_4Cl, HR rose 24±1.1%*. The rise in AVP during NH_4Cl was linearly correlated with pHa, r=-.67 (p<.0001, n=37), and PaO_2 tended to rise. In only one animal (not included), with pH=7.12 and PaO_2=12mmHg, AVP rose >8µU/ml, 30.2µU/ml. We conclude that: 1) acidosis, like hypoxemia alone, does not result in marked fetal AVP release; 2) whereas AVP release is related linearly to pHa, there appears to be a threshold value for PaO_2; and 3) acidosis and hypoxia appear synergistic for AVP release, but the role of $PaCO_2$ is unknown. *p<.05.

● 252 GLYCOGENOLYTIC EFFECTS OF THE CALCIUM IONOPHORE A23187, BUT NOT VASOPRESSIN OR ANGIOTENSIN, IN FETAL RAT HEPATOCYTES. Michael Freemark and Stuart Handwerger, Duke Univ. Med. Center, Dept. of Pediatrics, Durham, N.C.

Vasopressin, angiotensin II and phenylephrine stimulate glycogenolysis in postnatal rat liver by a non-cAMP, calcium-mediated mechanism. To determine whether these hormones also promote glycogenolysis in fetal liver, we have examined their effects, and those of the calcium ionophore A23187 (A), on glycogen metabolism in cultured fetal rat hepatocytes. Vasopressin and angiotensin (10^{-10}-10^{-7}M) had no effects on either ^{14}C-glucose incorporation into glycogen or phosphorylase a activity. However, A at concentrations of 1 and 10 uM inhibited glycogen synthesis by 31.3 and 89.1 percent, respectively (p< 0.001) and stimulated phosphorylase a activity by 66.9 and 184.1 percent respectively (p< 0.01). Incubation of cells in calcium-deficient medium markedly attenuated the effects of A on glycogen synthesis. As in postnatal liver, glucagon (1 and 20 nM) and isoproterenol (1 and 10 uM), which activate adenylate cyclase, inhibited glycogen synthesis and stimulated phosphorylase a activity in fetal hepatocytes. The minimal effective concentration of phenylephrine was 10 times that of isoproterenol. These results indicate striking differences in the ontogeny of cAMP-mediated and non-cAMP, calcium-mediated processes which regulate hepatic glycogenolysis. Since increases in cytosolic calcium induce glycogenolysis in fetal rat liver, the weak or absent responses to vasopressin, angiotensin and α-adrenergic agonists may result from defects in hormone-receptor binding or in postreceptor events leading to the mobilization of intracellular calcium stores. NIH grants HD07447 and HD06301.