

**336** CALCIUM (Ca) METABOLISM DISTURBANCES DUE TO PHENOBARBITAL (PB) DURING PREGNANCY IN EPILEPTIC MOTHERS AND THEIR INFANT. Catherine DOLISI\*, Louis DAVID\*\*, Marie C. CHAPUIS\*\*, Paul VERT\*. \*Centre Rech. Biol. Dev. Humain. Université de NANCY. \*\* U 234 INSERM LYON. FRANCE.

Chronic PB treatment may induce vitamin D (D) deficiency with a risk for osteomalacia. Looking for similar risks during pregnancy, 11 epileptic mother-infant pairs (E) were compared to 11 mother-infant controls (C) matched for age, parity, gest. age, birth-weight and season of birth, all without D or Ca supplement. Samples were taken at birth from the mother and the cord, and from the infant on day 2 and 7 for Ca, alkaline phosphatase (AP-bone isoenzyme), 25(OH)D (competitive protein-binding R<sup>3</sup>-assay) and iPTH blood levels. Ca level in E mothers ( $\bar{X} \pm SD$ ) is 86.0  $\pm$  2.4 vs 90.6  $\pm$  2.8 mg/L in C (P < .05). All E and 7/10 C mothers show 25(OH)D levels below the normal mean. Cord blood Ca is 99.8  $\pm$  5.2 mg/L in E vs 104.8  $\pm$  5.3 in C infants (NS). In the 1st week 6/11 E infants had at least one hypocalcemic level vs 0/11 in C (P < .01). Increased AP in cord blood (7.4  $\pm$  2.5 BU in E vs 5.4  $\pm$  1.1 in C (P < .05) were correlated with mothers blood levels (P < .01). On day 6 iPTH rose in E infants (P < .05). At birth 25(OH)D level is 17.6  $\pm$  7.1 in E and 19.2  $\pm$  1.7 ng/ml in C (NS) below the standard mean and correlated with mothers levels (P < .05). Abnormal values for all measurements (Ca, AP, D, PTH) were more frequent in group E (P < .05 in mothers, P < .01 in infants) than in group C.

It is suggested that PB treatment during pregnancy induces Ca metabolism impairment, a deficiency in D being partially compensated by regulatory mechanisms.

**337** GLUCOSE UTILIZATION IN ADULT RAT BRAIN FOLLOWING NEONATAL TREATMENT WITH MORPHINE, A QUANTITATIVE AUTORADIOGRAPHIC STUDY. Diana L. Dow-Edwards and Gail E. Handelsmann (Spon. by Audrey K. Brown) SUNY Downstate Medical Center, Department of Neurosurgery, Brooklyn, NY, and National Institutes of Health, National Institute of Child Health and Human Development, Laboratory of Developmental Neurobiology Bethesda, MD.

Previous experimental evidence has shown that neonatal exposure to morphine has lasting effects on pain thresholds and the density of opiate receptor sites in several brain regions (Handelsmann & Quirion, European J Pharmac., in press). In order to more clearly define the functional correlates of the altered distribution of opiate receptors, we chose the autoradiographic <sup>14</sup>C Deoxyglucose method for measuring in vivo glucose utilization rates in brain tissue (Sokoloff et al., J Neurochemistry 28:897-916, 1977). Newborn albino rats were injected s.c. with 1ug morphine sulfate in 5ul phosphate buffered saline each day on postnatal days 1 through 7. The deoxyglucose experiments were performed after the rats were 3 months of age. The frozen brains were sectioned 20microns thick and used to produce images on Xray film. Optical densities were obtained using a computerized image processing system. Glucose utilization rates were altered in several brain regions when compared to control values. Notably the reduced glucose metabolic rate found in the dentate gyrus of the hippocampus correlated well with the altered density of opiate receptors in that structure.

**338** AGE AND DOSE DEPENDENT PULMONARY VASCULAR CHANGES WITH PGD<sub>2</sub> IN CHRONICALLY INSTRUMENTED LAMBS. Willie H. Drummond, Hugh H. Shrager, Wendy A. Dalley, September L. Evans, University of Florida, Department of Pediatrics, Gainesville, Florida.

We operated 17 newborn lambs at <24 hours to place indwelling catheters in the aorta (AO), pulmonary artery (PA), left atrium (LA) and inferior vena cava (IVC), a flow transducer around the main PA and to ligate the ductus arteriosus. The lambs were studied on alternate days during normoxia and hypoxia at age 2-3 days (n=9), 9-13 days (n=12), and >21 days (n=11) with .01, 1, and 10 ug/kg PGD<sub>2</sub> given in random order as a 1 minute infusion. We measured maximal change in systemic, pulmonary, and left atrial (SAP, PAP, and LAP) pressure, cardiac output (CO), and we calculated systemic (SVR) and pulmonary vascular resistance (PVR) and PVR/SVR. Decreased PVR was found only in young lambs with hypoxia

AGE	BASE	.01	1	10	Increased PVR occurred
2-3	.19 $\pm$ .02	.18 $\pm$ .01	.19 $\pm$ .03	.20 $\pm$ .03	with PGD <sub>2</sub> during
9-13	.16 $\pm$ .02	.16 $\pm$ .01	.16 $\pm$ .01	.19 $\pm$ .02*	normoxia but not
>21	.21 $\pm$ .03	.22 $\pm$ .03	.25 $\pm$ .04*	.30 $\pm$ .04*	hypoxia in the older lambs. At each dose,
2-3	.47 $\pm$ .06	.41 $\pm$ .04*	.36 $\pm$ .03*	.32 $\pm$ .04*	with both N and H, SVR
9-13	.35 $\pm$ .03	.29 $\pm$ .02*	.29 $\pm$ .03	.33 $\pm$ .04	either increased or did
>21	.27 $\pm$ .03	.25 $\pm$ .02	.27 $\pm$ .02	.27 $\pm$ .04	not change. Thus, PGD <sub>2</sub>
2-3	.30 $\pm$ .06	.27 $\pm$ .05	.25 $\pm$ .04	.22 $\pm$ .04*	might be useful in the
9-13	.19 $\pm$ .02	.19 $\pm$ .02	.19 $\pm$ .02	.18 $\pm$ .02	immediate neonatal per-
>21	.22 $\pm$ .02	.22 $\pm$ .02	.23 $\pm$ .02	.22 $\pm$ .07	iod for treatment of
2-3	.71 $\pm$ .03	.56 $\pm$ .06*	.45 $\pm$ .04*	.35 $\pm$ .04*	pulmonary hypertension,
9-13	.47 $\pm$ .04	.42 $\pm$ .03*	.38 $\pm$ .01*	.31 $\pm$ .02*	but very careful diag-
>21	.35 $\pm$ .02	.34 $\pm$ .03	.34 $\pm$ .02	.26 $\pm$ .02*	nosis and monitoring

will be mandatory.

**339** IMPIPENEM PHARMACOKINETICS IN CHILDREN. Dan Engelhard, Itamar Shalit, Harris P. Stutman, James Dice, and Melvin I. Marks. University of Oklahoma Health Sciences Center, Dept. of Pediatrics, Oklahoma City.

Impipenem (Im) (thienamycin, MK0787/MK0791), a new  $\beta$ -lactam antibiotic, has outstanding potency against gram positive, gram negative, aerobic and anaerobic bacteria, including *Pseudomonas aeruginosa*. Selected pharmacokinetic and safety parameters were studied in children in anticipation of clinical therapeutic trials. A single dose (10 or 25 mg/kg) of Im was given intravenously to eight children aged 2-12 years hospitalized and receiving conventional intravenous antibiotics for suspected or proven infection. Plasma samples were obtained at 1 min, 30 min, 1, 2, 4, and 6 hours after the completion of the Im infusion. Random urine samples were also obtained. Im concentrations were measured by high performance liquid chromatography. Interpretation of the data was based on a one compartment open model. Selected parameters (means  $\pm$  S.D.) are as follows:

Dose mg/kg	C <sub>p</sub> ug/ml	T <sub>1/2</sub> hr	AUC ug hr/ml	TPC L/kg/hr
10	18.75 $\pm$ 3.26	0.77 $\pm$ 0.06	22.12 $\pm$ 4.29	0.46 $\pm$ 0.08
25	40.38 $\pm$ 2.52	0.97 $\pm$ 0.21	63.95 $\pm$ 12.3	0.40 $\pm$ 0.08

No adverse clinical or laboratory effects were noted. Based on these data and Im's *in vitro* activity, a dose of 25 mg/kg, intravenously every 4-6 hours, would likely be safe and provide therapeutic serum and urine concentrations in clinical trials in pediatric patients.

**340** PHENYTOIN (DPH) TERATOGENICITY (T) IN THE AMERICAN SEA URCHIN (SU) ARBACIA PUNCTULATA. G. Steven Estus, Dorothy M. Frank, and Jeffrey L. Blumer, Case Western Reserve University School of Medicine, Rainbow Babies and Children's Hospital, Department of Pediatrics, Cleveland, Ohio.

We have studied DPH T using a SU model. T was scored as abnormal cleavage, premature hyaline membrane rupture, failure to hatch, lack of motility and/or lack of skeletal development. DPH was found to cause dose dependent T over a concentration range of 1-150 ug/ml with an ED<sub>50</sub> (20 ug/ml) comparable to the human therapeutic serum level. Adverse effects were seen as early as the first cell cleavage. Wash out experiments showed a critical period from 45 min. post fertilization (PF) until the onset of gastrulation; maximal sensitivity was 60-90 min. PF. To evaluate the role of reactive epoxide intermediates or O<sub>2</sub> radicals in DPH T, the modulating effects of  $\alpha$ -naphthoflavone, metyrapone, aminotriazole, styrene-, cyclohexene-, and trichloropropene-oxides, catalase and superoxide dismutase were tested. None had a consistent effect. Alternatively, DPH T might be mediated via direct nucleic acid interactions. To investigate this hypothesis, the structural requirements necessary for DPH T were examined. Hydantoin (H),  $\phi$ -H, alkyl- $\phi$ -H and 3-N-methyl-DPH were not T at concentrations up to 150 ug/ml, suggesting two  $\phi$  groups and an unhindered H ring are required for DPH T. Furthermore, we have established a relationship between the electronic effects of DPH  $\phi$  substituents, as quantitated by the Hammett relationship. The DPH analog potency was: 5-p-methoxy- $\phi$ -5- $\phi$ H < 5-p-methyl- $\phi$ -5- $\phi$ H  $\leq$  0. The 5-p-OH $\phi$ -5- $\phi$ H and p-OH-p-methyl-DPH were devoid of effects up to 150 ug/ml.

**341** ETHANOL-ASSOCIATED PLACENTO-TOXICITY: Na,K-ATPase ACTIVITY. Stanley E. Fisher, Mark B. Atkinson, (Spon. by M. Silverberg). North Shore Univ. Hosp., Cornell Univ. Med. Coll., Dept. Pediatrics, Manhasset, NY.

Ethanol (E) abuse during pregnancy may be associated with intrauterine growth retardation (IUGR), due in part to E-induced interference with placental transport of amino acids. Since this placental transport is energy dependent, we measured the effect of acute and chronic E exposure upon rat placental Na,K-ATPase activity. Acutely, term pregnant rats (n=8) were gavaged with 4 gm E/kg body weight (2.5 hr before sacrifice). Control (C) animals (n=4) received sucrose. Chronic E animals (n=5) were fed a liquid diet containing 6% E (v/v) throughout pregnancy. Controls were isocalorically pair-fed. All dams were sacrificed at 20 days gestation. A membrane fraction was prepared for each placenta and mean Na,K-ATPase activity was determined per litter. Maternal blood E levels were 319  $\pm$  27.8 mg/dl (mean  $\pm$  SE) for acute animals at sacrifice and 195  $\pm$  26.0 mg/dl throughout pregnancy for chronic animals. RESULTS: There was a significant decrease in Na,K-ATPase activity for the chronically E treated animals (C=55.0  $\pm$  7.4 vs. E=31.8  $\pm$  6.0 pmoles P/min/mg protein; p=0.05; paired t-test). However, there was no difference between acutely treated E and C placentae. CONCLUSION: Chronic, but not acute ethanol exposure causes a reduction in rat placental Na,K-ATPase activity. This may help explain the etiology of IUGR association with maternal ethanol abuse.