

EFFECT OF PIVAMPICILLIN TREATMENT ON METABOLIC FUEL CONSUMPTION. Bela Melegh, Denes Molnar, György Mészáros, Ildiko Boek, Gabor Kócsanyi, Maria Papi, Department of Pediatrics, University Medical School of Pécs, Pécs, Hungary.

During pivampicillin (PIVA) administration pivalate is liberated from the drug which can form an ester with Coenzyme-A and subsequently with carnitine. Primary pivaloylcarnitine loss causes carnitine deficiency and hypoketonemia. No data have been available on the effects of PIVA on the overall metabolism of humans.

In 8 children the basal RQ increased from 0.87 ± 0.01 to 0.97 ± 0.01 ($p < 0.05$) on the 3rd day of PIVA (3x500 mg) administration measured by indirect calorimetry. Marked decrease was found in the daily utilization of fat, 11.27 ± 0.17 vs 0.31 ± 0.17 g/kg/d, while the consumption of carbohydrates increased (4.00 ± 0.50 vs 6.20 ± 0.51). No change was found in utilization of nitrogen compounds, and the total energy utilized was not affected by the treatment. All of the above parameters showed normalization 3 days after the introduction of supplemental carnitine (3x1g) to the PIVA treatment.

The data show, that the PIVA treatment causes profound changes in metabolic fuel consumption, the inhibited fat oxidation was replaced by increased utilization of carbohydrates. Administration of carnitine can reverse these changes by aiding the elimination of pivalate.

IMPAIRED MICROBICIDAL CAPACITIES OF MONOCYTES AND MACROPHAGES FROM PATIENTS WITH GAUCHER DISEASE (GD)

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Because of the primary manifestations of GD are due to involvement of monocyte-derived cells, we studied functional activity of phagocytic cells from Gaucher patients. GD type 1 was diagnosed in three patients (7 yr-old male /Pt.1/, 8 yr-old male /Pt.2/, 25 yr-old female /Pt.3/). Killing of *S.aureus* by freshly isolated blood granulocytes (Gr) and monocytes (Mo), and monocyte-derived macrophages (MDM; obtained by culturing Mo for 5 d in Teflon beakers in DMEM medium) was studied in suspensions of bacteria (5×10^6 /ml) and phagocytic cells (5×10^6 /ml). Incubations of phagocytic suspensions were performed in the presence of 10% human serum for 120 min, under slow rotation (4 rpm), bacterial killing was measured by colony counts after disrupting phagocytic cells in liquid nitrogen. The results shown below indicated a decreased capacity of Mo to kill *S.aureus*, and the lack of any killing of bacteria by MDM, whereas killing of staphylococci by Gr were comparable to that of controls.

Patients	Killing (% of inoculum)			β -D-glucosidase activity of WBC nM/min/g protein
	Gr	Mo	MDM	
Pt.1.	87	62	0	36
Pt.2.	93	53	0	57
Pt.3.	N/D	N/D	0	40
Control	85-95	80-90	35-52	400-1000

These *in vitro* studies provide new data to the pathophysiology of Mo and macrophages whose β -D-glucosidase activity has been reduced. Our results further elucidate host defense mechanisms in patients with GD and indicate a decreased resistance to bacterial pathogens in these patients.

PULMONOLOGY

DEVELOPMENTAL LOCALIZATION OF HOX 2.1 PROTEIN IN MOUSE FETAL LUNG SUGGESTS A ROLE IN DETERMINATION OF CELL FATE. Maryann V. Volpe, Heber C. Nielsen, Tufts University School of Medicine and New England Medical Center, NEMC #97, 750 Washington Street, Boston, MA, USA.

Hox genes are regulatory genes in mice containing a highly conserved homeobox region which are thought to control embryonic and fetal development. We have previously reported that hox 2.1 mRNA levels in fetal mouse lung are maximum on day 16, decreasing thereafter. Here we report the developmental localization of hox 2.1 protein in mouse fetal lung. Mice (fetal days 14 to 18; adult) were sacrificed and lungs frozen in liquid N₂, cryosectioned and incubated with hox 2.1 polyclonal antibody (courtesy of N. Wall at Vanderbilt U.) followed by alkaline phosphatase immunostaining. Staining increased with gestation, was rare in adult specimens and was not seen in the absence of primary antibody. Nuclear staining was localized to subepithelial mesenchyme on day 14 and to both subepithelial mesenchyme and adjacent epithelial cells on day 15. As gestation progressed, staining localized to terminal bronchiolar columnar epithelium, abruptly decreasing or disappearing at branch points with transition to flattened epithelium. In conclusion, the change in localization of hox 2.1 protein from subepithelial mesenchyme to regionally restricted epithelia suggests a role in the determination of epithelial cell fate and differentiation. The discordance between changes in mRNA levels and protein immunostaining suggests that hox 2.1 is complexly regulated during lung development.

DEVELOPMENT OF THE CAROTID BODY (CB) CATECHOLAMINE (CA) RESPONSE TO HYPOXIA IN RABBITS. Jean-M Hascöët, Aida Bairam, Jean-M Cottet-Emard, Eric Thorin, Jean-M Piquignot, François Marchal, Laboratoire Physiologie-Faculté Médecine, INSERM U272 Nancy; and CNRS 1196 Lyon-France. The ventilatory response to hypoxia has been related to the CB chemosensitivity. Changes in the chemosensory response observed in the postnatal period might be related to changes in the release of Dopamine (DA) and Norepinephrine (NE) from the CB as both are considered to be neuromodulators of the CB chemosensitivity. METHODS: 5 groups of rabbits aged $\leq 1, 5, 15, 25$ days and adults had their CB surgically removed under anesthesia, and 100% O₂. The CB were immediately infused in 400 μ l of nutritional media (HEPES+EDTA) for 1h at either 100% O₂ (Control, n=7,28,16,16,4 respectively) or 8% O₂ in N₂ (Hypoxia, n=10,27,20,16,3 respectively) at 37°C. CA content in the CB and the media was measured by HPLC. RESULTS: DA, NE (pmol) and fraction released in media (%) (mean \pm SD). (*: p < 0.05 vs control)

Age	≤ 1 d	5 d	15 d	25 d	Adults	p (vs age)
Control	DA	35 \pm 14	34 \pm 20	56 \pm 26	86 \pm 81	246 \pm 158 0.001
	Media	25 \pm 17	30 \pm 28	29 \pm 16	16 \pm 25	2 \pm 1 NS
	NE	19 \pm 11	20 \pm 9	32 \pm 30	86 \pm 74	112 \pm 69 0.001
Hypoxia	Media	20 \pm 8	25 \pm 22	18 \pm 12	7 \pm 9	2 \pm 1 0.003
	DA	61 \pm 17*	26 \pm 12	41 \pm 24	51 \pm 53	415 \pm 34 0.001
	Media	36 \pm 32	47 \pm 25*	47 \pm 31*	51 \pm 28*	12 \pm 3* 0.03
	NE	25 \pm 13	21 \pm 16	38 \pm 55	34 \pm 20*	219 \pm 164 0.001
	Media	30 \pm 27	33 \pm 23	28 \pm 21	30 \pm 17*	6 \pm 1* 0.01

Acute hypoxia increased significantly the release of DA from 5d of age. NE release also increased in response to hypoxia, but only from 25d of age. In the hypoxic newborn (≤ 1 d), DA content was increased but not its release.

CONCLUSION: These data suggest that the variations in the chemosensory response during development could be associated with changes in CA balance and release.

Dexamethasone modulates the pulmonary cellular inflammatory response in neonatal chronic lung disease. Ashton MR and Hall MA, Department of Neonatal Medicine, Southampton General Hospital.

In a randomized double-blind placebo controlled study we examined the effects of dexamethasone (DEX) on inflammatory cells (ICs) in fluid from serial broncho-alveolar lavage (BAL) from infants at high risk of developing neonatal chronic lung disease (CLD).

Infants <32 weeks gestation, <1250g birthweight, and still oxygen and ventilator dependent at 12 days were recruited. DEX was given from 14 days of age, at 0.6mg/kg/day in a 2 week tapering course. 7 infants received placebo, and 7 DEX. 4 subsequent courses of DEX were studied. Mean IC concentrations and mean neutrophils and macrophages (as % of total ICs) were calculated for days -1 and 0, 1 and 3, and 5 and 7 for each baby; median \pm changes in the proportions of ICs were calculated for each group. Analysis of covariance was used to study the contribution of DEX to the changes.

Values are MEDIANS (interquartile ranges)
 CHANGE (neutrophils) CHANGE (macrophages)
 DAYS 1 and 3 DAYS 5 and 7 DAYS 1 and 3 DAYS 5 and 7
 PLACEBO -14.6 (70.8) -9.6 (84.2) -2.6 (94.2) +2.5 (88.9)
 DEX -42.9 (67.5) -5.6 (100.2) +17.4 (28.8) -5.9 (68.2)
 The regression coefficients (RCs) for the changes in neutrophils and macrophages produced by DEX were -20.2 (95%CI -38.2 to -2.1) and 23.2 (95%CI 6.6 to 39.7), respectively. There was a strong trend towards a fall in neutrophil concentration (RC -19.7 95%CI -41.8 to 2.5).

The data suggest that DEX affects the IC population of BAL fluid in CLD by reducing neutrophils, and not macrophages as has been suggested in a previous study.

EFFECT OF INTRAVENTRICULAR HEMORRHAGE (IVH) ON PULMONARY FUNCTION IN NEWBORN PIGLETS. T. Farstad and D. Dratlid, Depts. of Pediatrics and Surg. Res., Rikshospitalet, University Hospital, Oslo, Norway.

While pulmonary dysfunction is a known complication of severe head injury in adults, little is known about the effects of cerebral injury on pulmonary function in newborn infants. We studied the effects of IVH on respiration and pulmonary mechanics in newborn piglets. The animals were intubated and mechanically ventilated at low frequencies to allow for spontaneous breathing between mechanical breaths. Blood (8ml/100g estimated brain weight (100%)) was then infused into the lateral cerebral ventricle. Gas exchange, respiratory rate (RR) and intracerebral pressure (ICP) were studied until apnea. Results were (mean \pm SD, *p < 0.05):

	Baseline	100% volume	At apnea
MICP (mmHg)	4 \pm 2	38 \pm 8	56 \pm 15
RR (breaths/min)	48 \pm 36	51 \pm 53	211
MV (ml/min)/kg	276 \pm 103	236 \pm 124	2218*
PaCO ₂ (kPa)	5.1 \pm 0.8	5.6 \pm 1.3	9.0 \pm 1.9*
R (cm H ₂ O/l/sec)	27 \pm 13	43 \pm 25	55 \pm 17*
Cl (ml/cm H ₂ O)/kg	2.1 \pm 0.4	2.0 \pm 0.6	2.1 \pm 0.5

IVH primarily affects RR until apnea and reduces minute ventilation (MV). Cl did not change. The increased R might be caused by bronchial constriction or neurogenic pulmonary edema. The increased R might also be a factor in the need for increased ventilatory support in infants with IVH.