HEMATOLOGY & ONCOLOGY

565 NEW METABOLIC PRODUCTS OF L-CITRULLINE AND L-HOMOARGININE. Ronald W. Wilson, Richard Thompson, and Arthur F. Kohrman. Michigan State University, College of Human Medicine, Department of Human Development, East Lansing 48824.

Several clinical conditions associated with hyperammonemia are also characterized, in part, by elevated serum and urine levels of citrulline (C), homocitrulline (HC), and homoarginine (HA). Our previous studies on ^{14}C-ureido-HC revealed that HC was converted by rats and mice, and, in vitro, by L-amino acid oxidase to a cyclic derivative (Fed. Proc. 35:1478, 1976). We now report mass spectrometric data which indicate that an L-amino acid oxidase product of (C) is also cyclic.

L-HA is also converted by rats and mice, and in vitro, by amino-acid oxidase to yet another unreported compound. The HA metabolite does not react with ninhydrin but does form a hydrazone with dinitrophenylhydrazine, and thus, may be a straight chain molecule. Enzymatic studies suggest that these α-keto derivatives are formed, in vivo, by transamination reactions.

These newly discovered metabolites may represent significant pathways for the disposal of HC, C, and HA in clinical situations where they accumulate.

566 COMPARISON OF SERUM PYRUVATE-KINASE (PK) AND CREATINE-PHOSPHOKINASE (CPK) IN CARRIER DETECTION OF X-LINKED MUSCULAR DYSTROPHIES. Mayana Zatz, Larry J. Shapiro, Michael M. Kaback and David S. Campion. University of California, Harbor General Hospital, Department of Pediatrics and UCLA, Center for the Health Sciences, Dept. Med., Los Angeles.

Serum PK and CPK determinations have been carried out in 172 individuals, including 50 normal controls, 68 patients with a variety of neuromuscular disorders and 50 female relatives of patients with the X-linked forms of muscular dystrophy, to confirm clinical diagnosis and to evaluate heterozygote detection in potential carriers. In control individuals the mean activity($\pm$S.D.) for PK is 1.2$\pm$0.46μmol/ml/h(with no differences between the sexes) and for CPK 5.5$\pm$1.9 Sigma units for females and 8.6$\pm$5.0 for males. In 21 patients with Duchenne dystrophy the range of PK is 7.3 to 150.4, and in 9 with the Becker type from 2.5 to 148.7. All had significantly elevated CPK levels. Six patients with the facio-scapulo-humeral form of dystrophy(including one with a probable diagnosis) had increased PK levels, while only 3 had elevated CPK levels. In 8 obligate carriers of the Duchenne gene, 7 had levels above the normal range, and 5 had elevated CPKs. Increased PKs were found in 9 of the 16 mothers of isolated cases, 10 of 14 patients' sisters and 2 among 6 other female relatives. Only 7 females in these three groups had increased CPK activity. Two of 4 obligate carriers for the Becker gene had an increase in both PK and CPK. These data suggest that the combined use of PK and CPK determinations may enhance the capability to discriminate carriers of the X-linked muscular dystrophies.

567 VALINE TOXICITY IN INTERMITTENT BRANCHED-CHAIN KETOACIDURIA (BCKA) WITH ATYPICAL DECARBOXYLASE ACTIVITY William B. Zipf, Richard J. Allen, Virginia C. Hieber Univ. Mich. Hosp., (Neuro & Endo Sections) Dept Ped, Ann Arbor.

In BCKA, leucine (Leu) metabolites are generally considered the cause of the toxic encephalopathy. An infant with intermittent (I) BCKA (thiamine unresponsive) demonstrated severe CNS toxicity to valine (val). This child had marked symptoms with serum leu levels <7.0 mg%; 7 other children with classic (C)-BCKA had no acute symptoms with serum leu <10 mg%. Oral load tests (100 mg/kg) with leu, val and iso-leucine (i-leu) in 2 children with C-BCKA caused no symptoms; the same tests in the I-BCKA child caused severe transient obtundation, EEG changes, lactic acidosis and hypoglycemia with val but no effects with leu or i-leu. Peak serum levels for each amino acid were similar in all children and always >16.0 mg%. Cultured fibroblast from children with C-BCKA show increasing decarboxylase activity with increasing substrate concentrations for Leu-1-^{14}C and Val-1-^{14}C. In fibroblast cultures from the I-BCKA child, the leu response was similar, but different with valine:

substrate concentration	Activity - n moles $CO_2/10^6$ cells/hour					
	Leucine			Valine		
(M)	I-BCKA	nl	%nl	I-BCKA	nl	%nl
1×10^{-6}	0.022	0.069	32	0.004		
5×10^{-6}				0.029	0.053	55
1×10^{-5}	0.030	0.080	38	0.037	0.16	23
1×10^{-4}	0.070	0.092	76	0.043	0.25	17
1×10^{-3}	0.100	0.161	80	0.076	0.30	25

This variant form of BCKA has a unique neuronal toxicity to val not previously reported that correlates with in-vitro studies.

568 THE LIVER IN THE SCHWARTZMAN REACTION. Arturo J. Abalil, Gungor Karayalcin, Fernando Costales, Isodore Gubernick, Philip Lanzkowsky. Sch. of Med., Health Sciences Ctr., State Univ. of N.Y. at Stony Brook and Long Island Jewish-Hillside Med.Ctr., Dept. of Pediatrics, New Hyde Park, New York.

The effects of Gram Negative endotoxin (E. Coli 0111B4) on the liver of rabbits has been studied. In 22 animals 92% developed liver necrosis following two intravenous doses of 50 mcg per kg of endotoxin at a 24 hour interval. Of 91 animals 42 survived for more than 12 hours following a large single dose (250-1000 mcg per kg) of endotoxin administered slowly intravenously for an 8 hour period and most of these developed a generalized Schwartzman reaction (GSR) and hepatic necrosis. Of 20 animals given a single dose of 50 mcg per kg endotoxin 15 developed piecemeal necrosis associated with microthrombi. Before endotoxin was administered liver function tests (SGOT, SGPT, LDH isoenzymes, 5' nucleotidase, and serum albumin) in all animals and liver biopsy in the 10 rabbits in which this was carried out were normal. After endotoxin the liver function tests and coagulation tests (PT, PTT, platelets, factors I, II, V and VIII) and split products of fibrinogen (SPF) were abnormal. A mild to moderate decrease in factor VIII and a slight increase in SPF suggest that disseminated intravascular coagulation (DIC) participated in this reaction. Although most of the hemostatic alterations could be attributed to hepatic damage, these studies indicated a close interaction between liver dysfunction and DIC in determining the effects of Gram Negative endotoxin in these animals.

569 ANTITHROMBIN-III HEPARIN COFACTOR DEFICIENCY IN A FAMILY: BIOLOGIC ACTIVITY, ANTIGENIC LEVELS, AND CROSSED IMMUNOELECTROPHORETIC ANALYSIS BEFORE AND AFTER THERAPY. Daniel R. Ambruso, Linda J. Jacobson, William E. Hathaway. Univ. of Colo. Med. Ctr., Dept. of Ped., Denver.

Identification of a family affected by antithrombin-III heparin cofactor (AT-III) deficiency was made after diagnosis of the index case, a 15-year-old male, who suffered a cerebral thrombosis after a 2-year past history of thromboses in the lower extremities. The patient showed a marked resistance to heparinization after his cerebral thrombosis. The mother and the sister of the index case were also affected. Studies showed decreased biologic activity (A) and antigen by the Laurell immunologic technique (I) of AT-III in the index case (A=27%, I=47%), his sister (A=29%, I=47%), and his mother (A=40%, I=56%). The normal range (+2SD) is A=66-138% and I=79-115%. Crossed immunoelectrophoresis (CIE) in agar containing heparin of patients' plasma and recalcified plasma revealed a pattern of migration identical with normal. After anticoagulant therapy with coumarin, AT-III activity and/or antigen was increased: index case (A=45%, I=65%), his sister (A=28%, I=62%), and mother (A=79%, I=88%). CIE on plasma and serum of the affected patients on coumarin were identical in pattern to a normal control on coumarin. In this family, the levels of AT-III activity and antigen were proportionately reduced and there appeared to be no qualitative differences in the AT-III molecule on CIE. Interestingly, both the AT-III activity and antigen increased on anticoagulant therapy with coumarin.

570 THE COMBINED HYPOTRANSFERINEMIA AND LOW UNSATURATED IRON BINDING CAPACITY IN EARLY PRETERM NEWBORN INFANTS. H.Bard, L.Medou, F. Teasdale, B.H.Doray, H.M.Schulman, Univ.of Montreal Ste.Justine Hosp., Dept.Ped.,& Jewish General Hosp., Lady Davis Inst. for Med.Res., Montreal,Que,Canada.

The serum iron binding protein transferin when iron free has been known to possess bacteriostatic & fungistatic activities. Many pathologic states in which the saturation of transferin with iron is elevated are associated with an increased occurance of infection. Since early preterm newborn infants are particularly susceptible to infection and iron supplementation is suggested by some authors, the aim of this study was to examine the saturation of transferin levels in the sera of extremely premature infants during the first few months of life. Transferin concentration & iron saturation were determined in 19 normal preterm newborn infants born before 32 wks of gestation at 2 wks interval until 5-6 wks of age. The data obtained showed that transferin levels increased from 51 to 63% of adult values & the percentage of the transferin saturated with iron only decreased from 93 to 83%. The prolonged hypotransferinemia & high iron saturation of transferin demonstrate that iron supplementation is unwarranted in early preterm infants during this period The harmful side effects of iron may include an increased susceptibility to infections.