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METABOLISM OF VALINE IN HUMAN CULTURED SKIN FIBROBLASTS. W.G. Ng, J. Oizumi, G.N. Donnell, and P. Fennessey. Childrens Hospital of Los Angeles, Los Angeles, Ca. and University of Colorado Medical Center, Denver, Co..

In vivo experiments of Ando, et al. and Tanaka, et al., in man have suggested that the metabolism of L-valine (val) to methylmalonate (mma) is via propionate (pro). In the present study, evidence has been gathered supporting this pathway from oxidation studies in cultured skin fibroblasts from normal individuals and patients affected with propionic acidemia and methylmalonic aciduria. Differentially labeled substrates (DL-val-2-C14, -4-C14; isobutyrate-1-C14, -2-C14) were incubated separately with intact cells. Volatile labeled CO_2 was determined and non-volatile organic acids were extracted and chromatographed. Nearly normal amounts of labeled CO_2 were liberated using val-2-C14 and isobutyrate-1-C14 by patients cells when compared to controls. Substantial amounts of a labeled non-volatile intermediate, presumably B-hydroxyisobutyric acid (B-hiba) were detected in all incubations. In the presence of methylene blue the amount of B-hiba was reduced with concomittant increase in CO_2 production. These findings support that the metabolism of val to mma is via the intermediates of B-hiba, methylmalonic acid semialdehyde (mas) and pro rather than through mas to mma directly.

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EFFECTS OF THE CONCEPTUS ON GLUCOSE KINETICS DURING FASTING IN PREGNANCY. Edward S. Ogata, Lance K. Sanders, Boyd E. Metzger, and Norbert Freinkel (spon. by Henry L. Nadler), Northwestern University Medical School, Prentice Women's Hospital and Maternity Center, Departments of Pediatrics, Obstetrics and Gynecology, and Medicine, Chicago.

Although hypoglycemia during maternal fasting in late pregnancy has been ascribed to continuing glucose loss to the conceptus, documentation in non-ruminants has not been secured. Therefore, glucose kinetics after one-day fast were measured in conscious, unrestrained pregnant rats (day 18 and 19 gestation) and age-matched virgin controls. Equilibrium infusions with glucose-6-^{14}C and glucose-6-^{3}H were instituted to assess recycling as well as total glucose turnover. As judged by gluc-6-^{3}H, total glucose turnover was augmented 42 % in fasted gravid animals (20.3 ± 2.2 vs. 14.3 ± 1.7 μmoles/min; $p < 0.001$). This was not attended by disparate recycling since net glucose utilization (as tested with gluc-6-^{14}C) was increased 49 % (15.2 ± 1.2 vs. 10.2 ± 1.4 μmoles/min; $p < 0.001$) and paired ratios for ^{14}C/^{3}H glucose turnover were similar in pregnant and control rats (0.78 vs. 0.80). Glucose turnover did not correlate with blood sugar, nor total body weight in non-gravid or extrauterine body weight in gravid animals. However, net glucose utilization correlated significantly with the mass of the whole conceptus ($r=0.744$; $p < 0.001$). These data indicate that glucose utilization is enhanced during dietary deprivation in late pregnancy in non-ruminants despite prevailing hyperlipacidemia. The phenomenon appears to be linked to the potential for glucose removal by the conceptus and thus represents an ever-increasing stimulus to extrauterine glucose conservation.

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EFFECT OF PLACENTAL LACTOGEN AND INSULIN INFUSIONS ON UTERINE GLUCOSE METABOLISM. Charles L. Paxson,Jr. Univ. of Neb. Med. Center. Omaha, Neb. (spon by G. C Rosenquist)

We have previously shown that placental lactogen induces an increase in uterine glucose uptake (Q). These studies were designed to determine the combined effects of insulin and placental lactogen (PL) on Q.

Five pregnant near-term Western ewes were chronically prepared by placement of catheters and electromagnetic flow probes. Following baseline studies, all ewes received infusions of PL and insulin. Initial infusions of insulin were also followed by superimposed "pulses" of PL.

Initial infusions of insulin and PL produced significant increases in Q, but no changes in maternal glucose or in uterine blood flow. The insulin increased Q, peaked at 1 hr of infusion and slowly decreased, although Q remained consistently above baseline values. The PL "pulse" infusions produced no further rise above the insulin elevated Q.

We conclude that both insulin and PL regulate uterine metabolism in the near-term pregnant ewe. The failure of PL pulses to further augment the insulin induced Q peaks may indicate the presence of common PL-insulin receptors which become "saturated" by the initial infusions, or the ratio of insulin to PL may be an important determinant of uterine glucose uptake.

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NO DIFFERENCES DETECTED SPECTROPHOTOMETRICALLY BETWEEN BLOOD PEPTIDES OF CYSTIC FIBROSIS AND NORMAL INDIVIDUALS FRACTIONATED BY COLUMN CHROMATOGRAPHY. Owen M. Rennert, Thomas W. Seale, Wai-Yee Chan and Marinus Flux. University of Oklahoma Health Sciences Center, Department of Pediatrics, Oklahoma City, Oklahoma.

Bioactive factors affecting ciliary activity, leucocyte degranulation and Na^+ resorption appear to accumulate in fluids of cystic fibrosis (CF) patients. We have investigated the presence of abnormal amounts or species of polypeptides (m.w. ≤ 20,000 daltons) in serum and plasma of 10 CF patients as compared to 10 age, sex matched normals and contrast patients. Freshly prepared citrated plasma or serum was fractionated by column chromatography on a Biogel P10 column (2.5x53cm) or Sephadex G50 column (2.5x100cm), eluted respectively with 0.1 M NH_4HCO_3 (pH8.3) or 0.01 M PO_4 buffer (pH7.4), and the elution profile monitored at 220nm. Six distinct peaks (m.w. 2-10,000) occurred in remarkably constant proportions in both CF and non-CF plasma specimens, while serum from each contained only 5 peaks. No consistent differences in amounts of these species were detected in cystics nor were any new peaks present. Further fractionation of major peaks on DEAE-Sephadex A25 gave no evidence of differences in the plasma peptide profile of cystics vs. normals. Based upon peptide standards of known m.w., the sensitivity of this spectrophotometric method is in the range of 0.5-5 nmole/ml blood. Therefore, if novel polypeptide factors do exist in CF, their concentration is below this level.

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CALCITONIN (CT) INHIBITS AND PARATHYROID HORMONE (PTH) ENHANCES THE MOBILIZATION OF LEAD-203 (^{203}Pb) IN THYRO-PARATHYROIDECTOMIZED (TPTX) RATS. John F. Rosen, Albert Einstein Coll. Med., Montefiore Hosp. & Med. Ctr., Dept. Ped., New York.

Previous results in TPTX rats infused with PTH have shown marked redistribution of ^{203}Pb in hard and soft tissues with a transiently small increase in urinary Pb excretion. Since $CaNa_2$-EDTA (EDTA) produced rapid depletion of bone ^{203}Pb coincident with a large increase in urinary Pb excretion, this study was undertaken to define further the interactions of EDTA, PTH, and CT on the tissue distribution of ^{203}Pb. Once 25μCi ^{203}Pb were given IV, TPTX rats were placed in metabolism cages; and 4 days later, EDTA, EDTA+PTH, or EDTA+CT were infused by a catheterized tail vein for 6H. Animals were sacrificed at 6 and 48H; and the results were expressed as the cpm Treated (T)/EDTA (E) Ratios, where * = $p < .01$, different from E:

	Hrs.	URINE	KIDNEY	LIVER	BRAIN	BONE
PTH+EDTA-T/E	6	1.76±.11*	.69±.04*	.24±.06*	.45±.10*	.62±.05*
	48	1.70±.06*	1.95±.10*	1.66±.14*	1.39±.07*	.95±.05
CT+EDTA-T/E	6	.88±.10	.54±.05*	.90±.10	.94±.06	.97±.11
	48	.92±.07	1.08±.14	1.21±.14	.95±.05	.97±.05

These data indicate that CT inhibits EDTA's actions by blocking removal of ^{203}Pb from bone. PTH, however, markedly enhances the effects of EDTA by increasing depletion of ^{203}Pb from bone primarily, with subsequent redistribution of ^{203}Pb to soft tissues. These dramatic effects of PTH may be of considerable clinical importance in modifying, to an extent, the toxic activities of Pb.

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THE EFFECTS OF GLUCOCORTICOIDS AND VITAMIN A (VA) ON LEAD-203 (^{203}Pb) TRANSPORT IN BONE ORGAN CULTURE. John F. Rosen, Albert Einstein Coll. Med., Montefiore Hosp. & Med. Ctr., Dept. Ped., New York.

A mobile compartment of bone Pb, regulated like bone mineral, has been demonstrated in vitro. Since the activation of lysosomal enzymes plays an important role in parathyroid hormone (PTH) effecting bone resorption, the importance of lysosomal labilizers (PTH, VA, $CaNa_2$EDTA [EDTA]) and stabilizers (glucocorticoids = cortisol [COR]) were assessed on the transport of bone Pb. Pregnant rats on day #18 of pregnancy were injected with 500μCi of ^{203}Pb and 200μCi of ^{45}Ca. On day #19, fetal bones were cultured in a chemically defined medium to which lysosomal labilizers and stabilizers were added. After 5 days in culture, ^{203}Pb and ^{45}Ca released from bones into the above experimental medium (EM) were compared to that released from bones into the appropriate control medium (CM). The ^{203}Pb results (* = $p < .01$, different from 1.00) were expressed as cpm EM/CM ratios:

1)PTH	2)PTH+COR	3)EDTA	4)EDTA+COR	5)VA	6)VA+COR
2.25±.09*	.63±.04*	2.55±.10*	.45±.08*	1.96±.10*	.95±.10

Significant release of ^{45}Ca occured in #1 and #5; and significant increases in medium levels of hydroxyproline and acid phosphatase were measured in #1, 3 and 5, but not in #2, 4 and 6.

These data indicate that: 1) lysosomal mechanisms play an important role in the release of ^{203}Pb from bone explants in vitro; 2) other agents, besides calcium-regulating hormones, control, in part, bone Pb metabolism in vitro, and 3) such agents (COR, VA) may well modify Pb's toxic effects in vivo.