## ● 1534 EFFECT OF CHRONIC METABOLIC ACIDOSIS ON THE RENAL METABOLISM OF 25-OH-D3 IN THE PERFUSED KIDNEY.

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Chronic acidosis has been shown to influence the renal metabolism of 25-OH-D3 in the intact rat. In this study we asked the question whether the pH of the animal directly influences activities of 1- and 24-hydroxylases. Acidosis was induced in vit.D deplete [D(-)] and vit.D replete rats [D(+)] by feeding 3% $NH_4Cl$ in drinking water for 9 days. Using an isolated perfused kidney system, we compared 1- and 24-hydroxylase activities (in fmole product/hr/g. tissue) in kidneys from D(-) and D(+) rats respectively. Results are Mean ± SEM.

| Diet | Group | n | Blood pH | Enzyme | Enzyme Activity | P |
|---|---|---|---|---|---|---|
| D(-) | Control | 15 | 7.33±0.01 | 1-OHase | 12.42±0.48 | < 0.05 |
| D(-) | Acidotic | 6 | 7.11±0.03 | 1-OHase | 7.93±1.70 | |
| D(+) | Control | 11 | 7.39±0.02 | 24-OHase | 6.82±0.70 | N.S. |
| D(+) | Acidotic | 3 | 7.06±0.04 | 24-OHase | 8.09±2.10 | |

Acidosis significantly inhibited 1-hydroxylase but not 24-hydroxylase activity. This change in 1-hydroxylase activity correlated directly with blood pH ($r=0.79$, $p<0.001$). Although blood ionic Ca was higher in D(-) acidotic rats (0.83±0.03 mM) compared with controls (0.58±0.04 mM), 1-hydroxylase activity did not correlate significantly with blood ionic Ca ($r=0.48$, $0.10>p>0.05$). We conclude that an increase in $[H]^+$ concentration directly suppress 1-hydroxylase activity but does not suppress 24-hydroxylase activity.

## ●1535 RENAL AND VASCULAR RESPONSES TO CONVERTING ENZYME INHIBITION (CEI) DURING FETAL LIFE.

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The renal and vascular responses to a continuous infusion of captopril (5 µg/min/kg) were studied in 2 groups of chronically catheterized fetal lambs (10 <120 days, 9 >130 days gestation; term 145 days). The infusion of CEI completely blocked the rise in fetal arterial blood pressure (MABP) following a bolus of angiotensin-I (1 µg). In both groups plasma angiotensin-II (A-II) decreased significantly ($p<0.05$) from 35±16 to 29±11 pg/ml in fetuses <120 days and from 33±5 to 21±3 in fetuses >130 days during CEI. A significant ($p<0.05$) rise in plasma renin activity (PRA) from 5.9±1.2 to 21.8±7.6 ng/ml/hr was found in fetuses >130 days during CEI; PRA did not increase in fetuses <120 days. The effect of CEI on renal blood flow (RBF), renal vascular resistance (RVR), filtration fraction (FF), glomerular filtration (GFR) and MABP was also studied.

| | <120 days | | >130 days | |
|---|---|---|---|---|
| | C | CEI | C | CEI |
| GFR ml/min | 2.89±0.28 | 2.58±0.31 | 3.96±0.18 | 4.34±0.28 |
| RBF ml/min | 45±4 | 46±5 | 48±4 | 53±6 |
| RVR $mmHg \cdot ml^{-1} \cdot min^{-1}$ | 0.94±0.08 | 0.86±0.08 | 1.02±0.22 | 0.77±0.07* |
| FF % | 9.4±1.1 | 8.5±0.8 | 12.0±1.6 | 12.7±1.5 |
| MABP mmHg | 44±1 | 39±2* | 52±1 | 44±1* |

(* for $p<0.05$ when control (C) compared to CEI) In summary, it is suggested that the renin-angiotensin system does play a role in controlling the blood pressure during fetal life and that the A-II feedback control of renin secretion is functional in fetuses >130 days gestation.

## 1536 EFFECT OF ANGIOTENSIN-II BLOCKADE ON GLOMERULAR AND RENAL HEMODYNAMICS DURING FETAL HYPOXEMIA.

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We previously showed, in fetal lambs >130 days gestation, that fetal hypoxemia produced a significant decrease in renal blood flow (RBF) which is closely related to a rise in plasma renin activity (PRA) ($r=-0.77$) (Circ Res, in press). The present study was designed to compare changes in glomerular and renal hemodynamics during fetal hypoxemia (HPX) to changes observed when fetal hypoxemia was produced during constant infusion of the converting enzyme inhibitor, captopril (5 µg/min/kg) (HPX-CEI). In both series of experiments (HPX and HPX-CEI) fetal $PO_2$ decreased from 24±2 to 15±1 mmHg and fetal arterial pH remained essentially stable at 7.36±0.01 before and during hypoxemia. Percentage (%) changes in glomerular filtration (GFR), RBF, renal vascular resistance (RVR), filtration fraction (FF), MABP and PRA during HPX in fetuses <120 days and >130 days were compared to % changes observed during HPX-CEI.

| | <120 days | | >130 days | |
|---|---|---|---|---|
| | HPX (N=11) | HPX-CEI (N=8) | HPX (N=11) | HPX-CEI (N=6) |
| GFR | -8±16 | -24±4 | -6±12 | -18±16 |
| RBF | -27±5 | -28±7 | -36±8 | -39±9 |
| RVR | +63±16 | +48±21 | +78±29 | +94±29 |
| FF | +61±29 | +31±13 | +48±16 | +49±11 |
| MABP | -0.4±2.5 | -5.6±4.5 | +10.2±3.7 | +5.5±5.2 |
| PRA | +9.3±14 | +42±37 | +65±20 | +552±195* |

(* for $p<0.05$ when HPX is compared to HPX-CEI.) The present data suggest that the renin-angiotensin system is not an important modulator of the renal and vascular responses during fetal hypoxemia.

## 1537 RENAL INVOLVEMENT IN FANCONI'S HYPOPLASTIC ANEMIA

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Fanconi's anemia is associated with multiple congenital anomalies. 28% of patients have renal abnormalities. We studied renal involvement in 2 boys and 3 girls aged 3-13 years with Fanconi's anemia. Chromosome numbers were normal but metaphases showed increased breaks and gaps in the 4 children studied. 3 children had significant growth retardation. 3 had enuresis. 1 girl had recurrent urinary infections. Initially, BP, BUN, serum creatinine, blood electrolytes, acid-base status, proteinuria, urinary concentration and acidification were normal in all. 3/4 IVPs were abnormal - bilateral small kidneys (one pelvic) with ureteric reflux (pt. 1); unilateral small kidney with ureteric reflux and clubbed calyces (pt. 2); small kidney with ureteric reflux and non-functioning small kidney on the opposite side (pt. 3). IVPs done at intervals showed no renal growth for 2 and 5 yr (pts. 2,3). Despite correction of low pressure reflux (pt. 3), renal failure was progressive. One girl (pt. 3) died awaiting renal transplant; 1 boy (pt. 4) died of unknown cause. Of the 3 children treated with androgens, 2 did not respond - 1 child died early in treatment, the other had advanced chronic renal failure. Conclusions: A variety of developmental renal abnormalities may be seen in Fanconi's anemia. Renal failure may be progressive. Anemia may respond poorly to androgen treatment if chronic renal failure is present.

## ● 1538 AMELIORATION OF TOXIC ACUTE RENAL FAILURE BY TREATMENT WITH THYROXIN.

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Thyroid hormone is thought to augment renal cellular and mitochondrial metabolism and has been shown to improve the enzymatic activity of tubular cell following mercuric chloride injury. To determine the effect of this hormone on the recovery from toxic acute renal failure, rats were injected, subcutaneously, with K-dichromate (15 mg/kg), a known tubular toxin. At the peak of the renal injury, 24 hours after injection, the animals were given, intraperitoneally, either thyroxin ($T_4$) 4 µg/100g BW (twice physiologic dose) or 0.5 cc of normal saline. Inulin clearance ($C_{in}$) was measured 24 hours later.

As expected, the 11 animals given normal saline had a significant fall of $C_{in}$ to 422.2 ± 27.2 µl/min/100g BW ($P < 0.001$ compared to control values, 1037.4 ± 48.6). In contrast, the 11 rats treated with $T_4$ had significantly improved recovery of $C_{in}$ to 678.2 ± 55.7 ($P < 0.001$). The same dose of $T_4$ given to sham-injected control animals failed to produce a similar increase in $C_{in}$ (1023.3 ± 33.1, P = NS).

These data suggest that treatment with thyroxin will significantly ameliorate the fall in $C_{in}$ following a toxic renal insult and that this effect is not due to a non-specific enhancement of glomerular filtration rate.

## 1539 BIG RENIN STIMULATION OF BLOOD PRESSURE, AND THE RENIN-ANGIOTENSIN SYSTEM IN THE NEWBORN PUPPY.

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Renin activity increases in vitro upon exposure to acid pH 3.3 followed by alkaline pH 7.4, low temperature, the proteases trypsin and pepsin, and urinary kallikrein. The purpose of this study was to determine the effect of big renin (M.W. 56,000, purified from human cord blood), on blood pressure (B.P.), the renin-angiotensin-aldosterone system, and renal function. One ug of plasma big renin was infused as an I.V. bolus in 10 newborn puppies. Mean aortic B.P. was monitored continuously. Blood samples for plasma renin activity (PRA), plasma aldosterone (pA), plasma cortisol (pC), Na, and creatinine (cr) were measured before and at 15, 30, 60, 90, and 120 min post-infusion; 30 min urine collections were measured for (cr), Na, and K. BP increased from 47.3 ± 1.0 mm Hg (M and SEM) to 57 ± 2.5 ($p<.02$), 30 min after the big renin infusion. PRA increased from 21.9 ± 2.4 ng/ml/hr to 63.6 ± 3.9 ($p<.001$), 30 min after the infusion. The pC level increased from 3.2 ± 0.6 ug/dl to 9.1 ± 2.1 ($p<.05$) 60 min after the infusion; pA did not increase. There was no change in ($C_{cr}$), electrolyte excretion, or plasma Na. Infusion of labeled big renin in five newborn puppies showed no chromatographic evidence of conversion to the lower-molecular-weight renin in the plasma or organ extracts. In conclusion: In the newborn puppy, 1) plasma big renin, M.W. 56,000, can raise the blood pressure, increase PRA, and pC, and 2) there is no evidence of plasma big renin conversion to renin.