●398 REGIONAL VARIATION IN ARTERIAL RESPONSE TO NOREPINEPHRINE DURING FETAL (F) AND NEWBORN (N) LIFE.

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Segments of renal and carotid arteries from F (129-139 days gestation; term 145 days) and N (5-7 days) sheep were mounted for isometric tension recording in Krebs solution at 37°C, aerated with 95% O_2 - 5% CO_2 gas mixture. After establishing optimal resting tension, changes in wall tension following cumulative additions of exogenous norepinephrine (NE) were studied. Contractile force generated was corrected for cross-sectional area of the segment (mN/mm2) and expressed as mean ±SE.

Dose NE (M)	F (n=5) Renal	N (n=5) Renal	F (n=6) Carotid	N (n=5) Carotid
10^{-7}	0.24±0.01	0.26±0.1	1.2±0.6	1.5±0.6
$3x10^{-7}$	0.7±0.2	1.12±0.5	2.2±0.9	3.1±0.8
10^{-6}	2.0±0.7	3.7±1.6	3.8±1.6	4.9±1.0
$3x10^{-6}$	5.5±1.6	9.4±2.9	5.1±1.4	7.3±1.0
10^{-5}	11.6±2.1	16.3±3.6	8.3±1.6	11.4±2.0
$3x10^{-5}$	14.8±2.1	24.5±3.2*	10.8±2.2	15.3±2.6
10^{-4}	15.0±2.2	28.1±2.4*	11.0±2.2	15.9±2.4

(*p<0.05, ANOVA) Results demonstrate that: 1) sensitivity to NE is unchanged in renal and carotid arteries from F to N life; 2) however, contractile force generated in the renal artery of N is greater than F, but no different in carotid arteries of F compared to N; and 3) developmental patterns of arterial responses to NE differ among blood vessels, suggesting that rapid changes in arterial smooth muscle reactivity to circulating catecholamines occur during the perinatal period.

399 DIRECT CYCLIC AMP (cAMP) STIMULATION OF RENAL VASODILATION IS GREATER IN FETAL (F) COMPARED TO NEWBORN (N) AND ADULT (A) SHEEP.

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We have previously demonstrated increased β-adrenoceptor mediated renal vasodilation in F compared to N and A sheep. The intra-cellular mechanism mediating this age-dependent β-adrenergic difference was studied by infusing forskolin, a direct stimulator of adenyl cyclase that bypasses the hormone-receptor interactions, into the renal artery of chronically instrumented F (129-139 days gestation; term 145 days), N (7-14 days), and A sheep to test concentration-dependent vasodilation. % changes (%Δ) in RBF velocity were measured by doppler flowmeter. Estimated concentration (M) of forskolin in renal blood ranged from 4 x 10^{-7} to 4 x 10^{-6} M, 3 x 10^{-7} to 5 x 10^{-6} M, and 2 x 10^{-7} to 3 x 10^{-6} M, in F, N and A, respectively. %Δ RBF ranged from 21±4 to 47±6 in F (n=5), 9±1 to 39±4 in N (n=5) and 11±2 to 36±3 in A (n=5), respectively. No difference was found between N and A (p=0.21). However, renal vasodilation was significantly greater in F compared to N and A (p=0.004), with a potency ratio F:N and F:A of 3:1. Results demonstrate: 1) an age-dependent cAMP mediated renal vasodilator mechanism; 2) that forskolin produces increased renal vasodilation in F compared to N and A; and 3) that differences in intra-cellular mechanisms may account in part for changes in renal β-adrenergic responses during development.

400 CODEINE AND MORPHINE LEVELS IN BREAST MILK AND NEONATAL PLASMA.

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Codeine (C) is often prescribed for post-partum analgesia. Little is known about C levels in colostrum and neonatal plasma (NP). We measured levels of C and its metabolite morphine (M) in breast milk (BM) and NP. Free C and M were measured by RIA sensitive to 0.5 ng/ml in NP and 2 ng/ml in BM. C dosing, 30 or 60 mg p.o., was determined by each woman's physician. Infants were full term, had 5 min. Apgars≥ 8, and had the following mean values: birth weight = 3.46 kg, age at sampling = 42 hrs., interval from dose to feed = 28 min. Mothers took a mean = 4.0 doses of C. BM concentrations of C (ng/ml) and M (ng/ml) in one woman after 60 mg of C were: 71.1 and 8.5 (½hr) 71.1 and 9.1 (1 hr); 199 and 11.2 (2 hr); 126 and 12.7 (4 hr). The rise in BM levels of M over 4 hrs might be explained by the binding affinity of BM for M. NP levels are presented below:

Hrs Post Feed:		1	2	4		1	2	4
Infant #1		1.7	-	3.3		0.8	-	2.0
	#2 Free C	-	3.1	4.4	Free M	-	1.8	2.2
	#3 (ng/ml)	4.3	-	-	(ng/ml)	2.2	-	-
	#4	4.5	1.5	-		1.9	1.0	-

In infants #1 and #2, C and M levels in NP rose over time. This may be due to slow absorption because of the large volume of BM and/or to enterohepatic circulation. The M/C ratio in NP of 0.54 is higher than the ratio in BM at feeding time of 0.15. The increased M/C ratio might be due to metabolism of C to M in neonates or greater conjugation of C than M. NP levels of C and M after a limited exposure are low and are probably safe.

401 EFFECT OF HISTAMINE (H) RECEPTOR BLOCKADE ON REPERFUSION INJURY IN THE RABBIT INTESTINE.

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Mast cells are abundant in the intestine and release H, an autocoid which has been implicated in the etiology of necrotizing intestinal disorders. We investigated the effect of histamine receptor blockers on reperfusion injury in the rabbit intestine. 25 rabbits underwent laparotomy under anesthesia. 8 were pretreated with IV Cimetidine (C), an H_2 blocker, (25 mg/kg), 9 with IV diphenhydramine (D), an H_1 blocker, (5 mg/kg), and 8 received no drug. In each, 4 intestinal loops were prepared: 2 loops were rendered ischemic for 5 mins., the other 2 loops serving as non-ischemic controls. The animals were sacrificed 4 hrs. after surgery. All intestinal loops were fixed and examined histologically by a single pathologist unaware of group assignment. Histological changes were graded.

	Ischemia			No Ischemia		
	C	D	No Drug	C	D	No Drug
Necrosis	14	14	12	10	11	2
No Necrosis	2	4	3	6	7	13

Irrespective of ischemia, the intestinal loops in rabbits pretreated with C and D demonstrated mucosal necrosis when compared to untreated animals ($p<0.001$, chi-square). These data suggest that blockade of both H_1 and H_2 receptor sites potentiated mucosal injury.

402 THE DETECTION OF HEROIN, COCAINE AND CANNABINOID METABOLITES IN THE STOOLS OF INFANTS OF DRUG DEPENDENT MOTHERS: CLINICAL SIGNIFICANCE.

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We have shown (Dev Pharm Ther 1:163, 1980) in morphine addicted fetal monkeys that the tissue concentration of morphine was highest in their intestines due to bile secretion or swallowed fetal urine. To test the corollary hypothesis that the stools from infants of drug dependent mothers (IDDM) will contain the drugs which the fetus has been exposed to, in utero, we collected stools (meconium) during the first 5 days from 10 IDDMs and 2 control infants and tested them for the metabolites of heroin (morphine), cocaine (benzoylecgonine), and cannabis (Δ 9 tetrahydrocannabinol or THC), three commonly abused drugs. In addition, we addicted a pregnant Sprague-Dawley rat by the daily subcutaneous injections of morphine sulfate (10-20 mgs/kg bid) from the 8th to the 21st day of gestation. Soon after birth, the rat pups were sacrificed and their intestines were collected for morphine analysis. The drug metabolites were extracted in appropriate solvents and quantitated by radioimmunoassay. The control stools were used for background correction. **RESULTS:** Four of the 10 IDDM stools contained morphine (range = 0.24-22.7 µg/gm stool, mean = 5.42) and 3 had cocaine metabolites (range = 0.24-0.67 µg/gm stool, mean = 0.42) up to the 2nd day of sampling. Five of 5 stools tested contained Δ 9 THC (range = 0.023-1.082 µg/gm stool, mean = 0.37) up to the 5th day sample. In the 9 rat pups, their intestinal contents collectively contained 1.65 µg of morphine or 0.18 µg morphine per pup. **SIGNIFICANCE:** This study shows that the stool (intestinal content) is a repository of the drugs which the fetus has been exposed to, in utero, and their detection may provide a unique insight into the drug exposure of the fetus throughout gestation. Likewise, since the complete evacuation of meconium occurs slowly, drug detection for diagnostic purposes in infants, is feasible even in late sampling.

●403 EVIDENCE FOR VASODILATORY DA_1 RECEPTORS IN THE PULMONARY VASCULAR BEDS OF RATS.

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The vasodilating effects of the post-synaptic, vascular dopamine receptor (DA_1) agonist, fenoldopam (Fen) on the systemic and renal vascular beds have been widely investigated. The effect of Fen on the pulmonary vascular bed is not well known. Using an isolated, in situ, salt perfused, isogravimetric rat lung preparation, we devised an experiment in which we infused Fen into the isolated lung during normotensive pulmonary artery pressure (PAP), during prostaglandin ($PGF_{2\alpha}$) induced pulmonary hypertension, and after DA_1 blockade with SCH 23390, during a hypertensive state. Four Sprague-Dawley rats were studied. For all experiments, PAP and LAP were directly measured while flow (Q) was maintained at a constant rate, (Q > 0.03 ml/kg/min). PVR was calculated, PVR = (PAP - LAP)/Q. ΔPAP and ΔPVR for all experimental conditions were evaluated by normal distribution analysis with a null hypothesis stating that PAP=0 and PVR=0. The null hypothesis is rejected at $p<0.05$. Data are presented as mean + SD. Fen infused during normotensive PAP caused no significant change in PAP (ΔPAP=-0.05±0.06 mm Hg) and PVR (ΔPVR=-0.001±0.002 r units). During a $PGF_{2\alpha}$ induced pulmonary hypertensive state, infusion of Fen significantly ($P<0.05$) decreased PAP (ΔPAP= -1.25±0.5 mm Hg) and PVR (ΔPVR=-0.41±0.028 r units). The DA_1 receptor antagonist, SCH 23390, effectively blocked the action of Fen during hypertensive PAP (ΔPAP=-0.08±0.3 mm Hg) and PVR (ΔPVR=-0.003±0.013 r units). Our results suggest that vasodilatory DA_1 receptors are present in the pulmonary vascular beds of rats, DA_1 induced vasodilation occurs during vasoconstrictive states, and the vasodilatory effect is blocked by DA_1 receptor blockade.