THE POSTNATAL ONTOGENY OF RAT UTERINE ORNITHINE DECARBOXYLASE

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Uterine ornithine decarboxylase (ODC) activity was maximally induced 6 hr after s.c. administration of 10 ug of various estrogens (estradiol, ethynylestradiol, diethylstilbestrol, and moxestrol, each in 10 ug sesame oil) to 5 day old S.D. rats. The antiestrogens tamoxifen (TAM) and clomiphene failed to increase ODC activity in 5 day old animals. Time course measurements were conducted over 24 hrs in control and E_2 injected animals on postnatal days 5, 10, 14, 20 and 28 and in 60 day old ovariectomized adults. An age dependent decrease in control and 6 hr E_2-induced activity was observed. However, there was progressive development by day 28 of a second peak of ODC activity at 15-18 hrs, which had the same Km for ornithine as the 6 hr enzyme peak. Rats were treated with TAM on postnatal days 1-5 or 10-14 at 10 ug/rat/day s.c. in 10 ul sesame oil, and uterine ODC responsiveness to E_2 over 24 hrs was determined on day 26. While control animals showed the typical biphasic response, both groups of TAM pretreated animals showed a significant reduction in the 18 hr but not the 6 hr ODC peak. Thus TAM interferes with the normal postnatal development of the E_2 induced biphasic ODC pattern.

Changes in Cytochrome P-450 and Subcellular Calcium Levels by Carbon Tetrachloride in Phenobarbital, Chlordecone and Mirex Pretreated Rats.

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Previous reports from this laboratory compared the potentiation of cytochrome P-450 destruction by CCl_4 in phenobarbital (PB) and chlordecone (CD) pretreated rats. This study was designed to establish the relationship between the destruction of cytochrome P-450 by CCl_4 and concomitant changes in subcellular calcium levels. Male Sprague-Dawley rats (200-225 g) were maintained either on normal diets or on diets containing 10 ppm CD, 10 ppm mirex (M) or 225 ppm PB. On day 15, the animals received a single ip injection of 100 µl CCl_4/kg in corn oil vehicle (1 ml/kg). Controls received only the vehicle. The rats were sacrificed at different time intervals (0-36 hr) following CCl_4 administration and liver microsomal cytochrome P-450 was measured. Total calcium was also quantitated in liver homogenate, mitochondria, microsomal and cytosolic fractions. A progressive decrease in cytochrome P-450 levels at 6, 12, 24 and 36 hr was observed in PB pretreated rats whereas animals maintained on diet containing M showed significantly lesser destruction. CCl_4 given to rats maintained on normal diet decreased the P-450 levels only at 12 hr and the levels returned to normal by 24 hr. A progressive increase in subcellular levels of calcium was observed. Total hepatic and mitochondrial calcium increased at 24 hr in normal diet + CCl_4 rats. The results suggest that the liver plasma membrane is sensitized in such a way so as to greatly perturb calcium pumping mechanism(s) in the presence of CCl_4 which would contribute to the potentiated hepatotoxicity. (Supported by ES-01369.)