AROMATIZATION OF NORETHINDRONE TO ETHYNYLESTRADIOL IN HUMAN ADULT LIVER [Poster 41]

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ABSTRACT: Homogenates of human adult liver are capable of aromatizing norethindrone (17α-ethynyl-19-nortestosterone) to ethynylestradiol (17α-ethynylestradiol). The evidence of ethynylestradiol formation was obtained using a Bio-Rad AG1-X2 column, thin-layer chromatography and co-crystallization.

INTRODUCTION: Norethindrone (17α-ethynyl-19-nortestosterone, ENT) is a derivative of 19-nortestosterone and is used widely as an oral contraceptive. ENT possesses a weak estrogenic activity as well as potent progestational action. The estrogenic activity is considered to be due to conversion of ENT to 17α-ethynylestradiol (EE_2) (1). Recently, some investigators have reported that ENT is aromatized to EE_2 in small quantities in human placental preparations in vitro (2,3). Although ENT has been confirmed to be aromatized enzymatically in human placenta, the organ where ENT is metabolized to EE_2 in non-pregnant humans after its oral administration is still unknown. Since liver contributes mainly to the metabolism of steroid hormones, we investigated whether or not the liver can transform ENT to EE_2 without the presence of acid or base.

MATERIALS AND METHODS: Human adult liver was obtained from patients with hepatoma at operation. The liver homogenate (1 g wet wt) in 10 mL of 1/15 M phosphate buffer (pH 7.4) was incubated with [6,7-^{3}H]ENT (435 pmol) and NADPH (5 mg) at 37°C for 2 h in air. After stopping of the enzyme reaction, [4-^{14}C]EE_2 (10,000 dpm, 500 μg) was added to the incubation samples. The steroids were extracted with ethyl acetate. The extract was applied to a Bio-Rad AG1-X2 column followed by thin-layer chromatography (4). The EE_2 area thus obtained was finally subjected to co-crystallization to constant specific activity and $^3H/^{14}C$ ratio of crystals. Our procedure does not involve the non-enzymatic chemical aromatization from ENT.

RESULTS: All samples (n=10) aromatized ENT to EE_2. The value of EE_2 formed from ENT was 24-1121 ($\bar{x}$=371) fmol/h/100 mg protein. Control samples had less than 10 fmol/h/100 mg protein. There was no significant correlation between the EE_2 values, age, and sex. These results demonstrated that human adult liver aromatizes ENT.

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