The Effect of Sex Hormones on the Activity of Tryptophan Oxygenase and other Corticosteroid-Inducible Enzymes in Rat Liver

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An increased capacity for the biosynthesis of nicotinic acid ribonucleotide has been observed during pregnancy (Brown, Thornton & Price, 1961) in women taking oestrogen–progestogen preparations for contraceptive purposes, and in normal human subjects receiving oestrogens alone (Rose, 1966). Women using oestrogen–progestogen types of oral contraceptive also exhibit a decrease in the concentration of plasma tyrosine (Rose & Cramp, 1970). These effects have been attributed to an increase in the activity of the corticosteroid-inducible enzymes tryptophan oxygenase (EC 1.13.1.12) and tyrosine aminotransferase (EC 2.6.1.5) with enhanced metabolism of the amino acids along degradative pathways (Rose & Braidman, 1970).

In an attempt to investigate this problem further, adult female rats were given 10μg of oestradiol benzoate daily for 14 days by subcutaneous injection. Controls were injected with a corresponding volume of the corn-oil vehicle. Highly significant increases were observed in the activities of liver tryptophan oxygenase, tyrosine aminotransferase and alanine aminotransferase (EC 2.6.1.2), a third glucocorticoid-inducible enzyme.

The role of the adrenal gland in these changes was demonstrated by the administration of oestrogens to adrenalectomized female rats. The activities of tryptophan oxygenase and alanine aminotransferase in the adrenalectomized control animals were lower than in intact controls and tyrosine aminotransferase activity was unchanged by adrenalectomy, as shown previously by Rosen, Harding, Milholland & Nichol (1963). After oestradiol benzoate administration, the adrenalectomized animals showed no increase in liver alanine aminotransferase and, although the activity of the other two enzymes was higher than in the controls, they were still significantly lower than in the livers of the intact female rats treated with oestrogen.

Control male rats had significantly lower tryptophan oxygenase activity than did females of comparable age and weight. Injections of 10μg of oestradiol benzoate for 14 days produced increased activity of liver alanine aminotransferase, as described by Keller, Richardson & Yates (1969), and also increased tryptophan oxygenase activity.

The importance of sex hormones in maintaining basal tryptophan oxygenase activity was further demonstrated by the effect of ovariectomy, which significantly decreased tryptophan oxygenase activity in females. Daily subcutaneous injections of 100μg of testosterone propionate administered for 14 days to intact female rats also resulted in decreased tryptophan oxygenase activity, not significantly different from that observed in intact male controls. Tyrosine aminotransferase activity remained unaltered.

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The Formation of Nitrosamines by Human Intestinal Bacteria

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The nitrosamines, a group of potent carcinogens that produce tumours in a range of sites in laboratory animals (Magee & Barnes, 1967), are produced by the action of nitrite on secondary amines under acid conditions. Sander (1968) demonstrated that four strains of nitrate-reducing enterobacteria could produce nitrosamines enzymically from nitrate and secondary amines at neutral pH values. We have confirmed this result using a number of strains of *Escherichia coli* isolated from the human intestinal tract, and have demonstrated that some non-nitrate-reducing strains of lactobacilli, group D streptococci, clostridia, bacteroides and bifidobacteria will nitrosate secondary amines with nitrite at neutral pH values. The nitrosamines were separated by t.l.c. and detected by spraying with sulphanilic acid and α-naphthylamine reagent after photolytic splitting to release the nitrite; quantitative assays were made by the polarographic method. The production of diphenylnitrosamine was confirmed from the i.r. spectra after purification by t.l.c.

The secondary amines nitrosated included dimethylamine, pyrrolidine and piperidine, all of which are present in normal human urine (Asatoor, 1960). The amount of nitrosamine formed is dependent on the basicity of the secondary amine, ranging from as much as 68% for diphenylamine to