88. Aromatization of androgens by human fat tissue

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The ability of human abdominal, breast and axillary fat to convert androgens into estrogens was investigated by incubating labelled substrates in the presence of NADPH with a variety of cell preparations. The incubation products were subject to phenolic partition, paper chromatography, methyl-ether formation, repeat chromatography and crystallization with cold reference standards to constant specific activity. Androstenedione was converted to estrone and, to a lesser extent, to estradiol-17β by crude homogenates, minces, fat-free particulate fractions (1000–100,000 g and isolated fat cells obtained from abdominal, breast or axillary fat. Testosterone was found to be aromatized as actively as androstenedione, but in this case more estradiol-17β was formed than estrone. 19-Hydroxyandrostenedione also served as substrate, giving results similar to those obtained with androstenedione. Fat tissue obtained from cancerous breasts was found to be as active as normal breast fat (1–4 pg/g fat/90 min) but lower than that of abdominal fat (3–27 pg/g fat/90 min). In each case in which axillary fat was compared to breast fat from the same subjecy, the activity of the axillary fat was 5 to 10 times higher. The results indicate a possible role of adipose tissue as a significant extra-gonadal source of estrogens. However, there is no apparent difference in activity between fat derived from normal and cancerous breast.

4. Steroid catabolism

4A 1. Steroid catabolism: Androgens—I

89. Androsta-1,4-diene-3,17,19-trione: Its provisional identification as a new placental metabolite of androstenedione

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In continuing an earlier study on C_{19} steroid metabolism by human placenta, [4-^{14}C] androstenedione was incubated with the 10,000 g supernatant at 37°C for ½ h. The neutral metabolites obtained were chromatographed on paper in cyclohexane: benzene (3:1 v/v)/propylene glycol. Radioactive scanning showed the presence of two new metabolites, I and II. From a comparison of its chromatographic mobility with those of reference steroids, it appeared that metabolite I is probably androsta-1,4-diene-3,17,19-trione. Evidence in support of this structure was obtained from the following experiments: (1) When 19-oxoandrostenedione was incubated, alone or together with [4-^{14}C] androstenedione, with the 10,000 g supernatant, there was formed, besides others, a metabolite with the chromatographic mobility of metabolite I: (2) When [4-^{14}C-1β,2β-^{3}H] testosterone was used as substrate, a significant loss of ^{3}H relative to ^{14}C was observed in the fraction of metabolite I, which was almost equal in magnitude to those in the oestrogen fractions. Provisional identification of metabolite I as androsta-1,4-diene-3,17,19-trione was based on the following degradation: Metabolite I $\xrightarrow{NaBH_4}$ the 19-hydroxy-1,4-diene-3-ketone $\xrightarrow{OH^-}$ Oestrone and/or Oestradiol.

90. Control of rat testicular 5α-reductase activity for testosterone and progesterone: blinding, X-irradiation, melatonin, prolactin, LH, and FSH

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Rat testicular 5α-reductase activity was estimated by the conversion of progesterone-4-^{14}C into the 5α-,3-keto and 5α-,3β-ol metabolites and via the Δ^4-reductase assay. Both steroids were reduced by rat testicular preparations. Whole-body irradiation (450 R) resulted in triphasic changes in the biotransformation of progesterone-4-^{14}C into 5α-pregnane-3,20-dione and 5α-pregnan-3β-ol-20-one by teased-tubular preparations. Moreover, these two enzyme activities were inversely related to each other, but were related to changes in melatonin synthesis by the pineal gland. Melatonin stimulated 5α-reductase *in vitro* at 10^{-9} M, but inhibited it at 10^{-5} M. Injections of melatonin into rats increased hypothalamic 5α-reductase activity, but had little effect on testicular 5α-reductase activity. Prolactin *in vitro* stimulated testicular 5α-reductase activity. H_2O_2 *in vitro* inhibited 5α-reductase activity. Studies involving blinding and injections of gonadotrophins showed that the control of 5α-reductase activity is complicated and that melatonin has antigonadotrophic activity. Moreover, the effect of melatonin on this enzyme is often masked by its effect on gonadotrophin secretion that in turn reduces the activity of this enzyme. (Supported by the U.S. Atomic Energy Commission grant no. AT(11–1)-1602.)

91. Testosterone 5α-reductase in rat skin homogenates

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Experiments were designed to find suitable conditions to determine the 5α-reductase activity in rat skin homogenates. The dihydrotestosterone formation was linear until 15 min. The enzyme activity was lost when the tissues or homegenates were frozen. The 5α-reductase was very heat labile at 37°C in absence of testosterone and NADPH since complete loss of activity occurred after 1 h of preincubation. At 0°C, there was a 20% decrease after 5 h. The enzyme activity was also measured in the skin at various anatomical sites. It was found to vary with each region in the following order in the male: tail > scrotum > ear > genital skin > dorsum ⩾ thorax > sole of the foot. In a few tissues, the enzyme activity was higher than in the prostate. Corresponding female tissues exhibited lower reductase activity except the sole of the foot in which the contrary was found. This significant sex difference indicates that sex hormones may be involved in the control of the levels of that enzyme in rat skin.