92. Conversion of testosterone-4-^{14}C into 5α-dihydrotestosterone in the human placenta *in vitro*

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Testosterone-4-^{14}C (T) was incubated with sections of the placenta and amnion and its conversion into 5α-dihydrotestosterone (DHT) was investigated. Added T-^{3}H and DHT-^{3}H following incubation served for the estimation of recovery, and the ratio $^{14}C/^{3}H$ was a comparative measure of quantitative estimation. Steroids were purified as follows: (1) thin layer chromatography (t.l.c.) on silica gel HF_{254} in the system of chloroform:methanol (99:1). (2) t.l.c. on silica gel in the system ethyl ether:benzene (70:30). (3) acetylation and t.l.c. on aluminium oxide in the system benzene:ethyl ether (80:20). (4) hydrolysis of acetates and crystallization. It has been found that amnion, in the presence of NADPH, converts T into DHT with a yield of about 0·7%, whereas placenta does not possess such properties. Furthermore it has been estimated that the quantity of unconverted T in amnion incubates is very high compared to low quantities in placental incubates. Further investigations of the problem are under way.

93. An unusual inherited form of male pseudohermaphroditism. A model of 5α-reductase deficiency in man

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We have investigated 12 families with 22,46 XY pseudohermaphrodites born with ambiguous genitalia. They masculinize at puberty without breast enlargement, have normal testes histologically, no Mullerian structures, complete Wolffian differentiation, small phallus, bifid scrotum, urogenital sinus with perineal hypospadias and blind vaginal pouch. Plasma testosterone (T) is normal; however, 5α dihydrotestosterone (DHT) is less than 2% of plasma T (normal 10%). During constant infusion of radioactive T, less than 1% is converted to DHT (normal 4–7%). The urinary 5β/5α androstane 17-ketosteroid (etiocholanolone/androsterone) ratio is markedly elevated. After glucuronidase hydrolysis, 7–14/1 (normal 0·4–2·0/1) – after glucuronidase and hot acid hydrolysis, 4·5–8·0/1 (normal 0·4–1·3/1). Urinary 5β/5α androstane (3α/3β hydroxy) 17β-hydroxysteroid ratio, 6·5–10/1 (normal 1·2–2·2/1). Analysis of pedigrees reveal inheritance as autosomal recessive. The clinical abnormality is expressed in males – one female studied shows the same biochemical defect. Carriers show a modest increase in urinary 5β/5α ratio. We postulate this condition as the distinct clinical entity of steroid 5α-reductase deficiency which may delineate the roles of T and DHT in sexual development. At a critical period in utero, masculinization of external genitalia may be DHT dependent, but Wolffian differentiation T dependent. The events at puberty may be mainly T dependent, with exception of facial hair and prostate growth which may be DHT dependent.

94. Localization of androgen metabolizing enzymes in human skin

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Human axillary skin rapidly metabolizes testosterone to the active androgen 5α-dihydrotestosterone; this may control hair growth and tissue differentiation in the axilla. Androstanediols and 17-oxosteroids are also formed. The distribution of steroid metabolizing enzymes in skin is of interest. Female axillary skin was dissected under a microscope after partial digestion with collagenase. Isolated tissue fractions were incubated with 7α-^{3}H testosterone in Krebs Improved Ringer I medium containing added cofactors. Testosterone metabolites were separated by chromatography and identified by reversed isotape dilution. The sweat gland fraction (mainly apocrine glands) contained 46% of the 17β-hydroxysteroid dehydrogenase, 90% of the 3α-hydroxysteroid dehydrogenase and 80% of the 5α-reductase. Other tissues (hairs, epidermis, sebaceous glands and residual dermis) contained lesser amounts of these enzymes. The apocrine sweat glands which are thought to be androgen controlled contain most of the testosterone metabolizing enzymes in axillary skin and form the most 5α-dihydrotestosterone. The other tissues also formed 5α-dihydrotestosterone though in the hair follicles androstenedione was the major metabolite.

95. Factors influencing the interconversion of androstenedione and testosterone in skin

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Human skin from different body sites exhibits characteristic patterns of androgen metabolism *in vitro*. Forehead skin rapidly converts testosterone to androstenedione but shows little activity in the reverse reaction; axillary skin actively converts androstenedione into testosterone. These differences could depend on the generation of NAD and NADP in the tissue or on the properties of the 17β-hydroxysteroid dehydrogenases. Incubation of slices of forehead and axillary skin under a variety of conditions expected to affect the generation of oxidized and reduced NAD and NADP did not alter the patterns of steroid metabolism. Homogenates of forehead and axillary skin only metabolized testosterone and androstenedione in the presence of added NAD^+ and $NADP^+$ (testosterone) or NADH and NADPH (androstenedione). NAD^+ and NADH were the preferred cofactors. In this system the same patterns of steroid metabolism were obtained as with whole tissue slices, suggesting that the differences in interconversion of testosterone and androstenedione may be due to the properties of different forms of 17β-hydroxysteroid dehydrogenase.

96. Studies on testosterone metabolism in liver and extrahepatic tissues of man

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The formation of hydrogenated C_{19}-steroids was investigated after incubation of (1,2-^{3}H)-testosterone (T) with tissue slices of human liver, skin, striated muscle, fat, lung, kidney, gastric mucosa and myometrium. Tissue slices of human liver, incubated without cofactors, transformed T in particular to 4-androstenedione(Δ^4-A,14-36%); 5α- or 5β-hydrogenated metabolites were formed only to a small extent. Liver slices, fortified by NAD/NADH, metabolized T to Δ^4-A(27–42%) and to 5β,3α-androsterone(5β,3α-A, 7–9%). With a NADPH-generating system T was metab-