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Inactivation of androgens by UDP-glucuronosyltransferase enzymes in humans

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In humans, 3β-hydroxysteroid dehydrogenase (3β-HSD), 17β-HSD and 5α-reductase activities in androgen target tissues, such as the prostate and skin, convert dehydroepiandrosterone, androstenedione and testosterone into the most potent natural androgen dihydrotestosterone (DHT). This androgen is converted mainly *in situ* into two phase I metabolites, androsterone (ADT) and androstane-3α,17β-diol (3α-DIOL), which might be back converted to DHT. Here, we discuss the recent findings regarding the characterization of specific UDP-glucuronosyltransferases (UGTs), UGT2B7, B15 and B17, responsible for the glucuronidation of these metabolites. The tissue distribution and cellular localization of the UGT2B transcripts and proteins in humans clearly indicate that these enzymes are synthesized in androgen-sensitive tissues. It is postulated that the conjugating activity of UGT enzymes is the main mechanism for modulating the action of steroids and protecting the androgen-sensitive tissues from deleteriously high concentrations of DHT, ADT and 3α-DIOL.

The gonads of both sexes are the main site for the production and secretion of testosterone into the circulation. In men, the production of testosterone by the testicles starts at puberty and remains relatively stable throughout life [1]. In women, the secretion of estrogens and progesterone by the ovaries also begins at puberty, with minimal amounts of testosterone and its precursor androstenedione (4-DIONE) secreted during the ovarian cycles; after menopause, very small amounts (if any) of androgens are produced by the ovaries [2]. For both sexes, small quantities of androgenic steroid precursors and testosterone are produced by the adrenals before adrenarche [3]. At this time, the growth of the adrenal zona reticularis is accompanied by an increase in secretion of androgen precursors, dehydroepiandrosterone (DHEA), its sulfate (DHEAS), androst-5-ene-3β,17β-diol and its sulfate, and finally, 4-DIONE [4]. The level of these serum adrenal precursors steadily increases up to $\sim$30 years of age; thereafter, it decreases markedly so that, at 60–70 years of age, levels are only 20% of those seen in the young adult [1].

Of all the androgens found in the circulation, only testosterone and its 5α-reduced metabolite dihydrotestosterone (DHT) activate the androgen receptor and modulate gene transcription [5]. In addition, DHT, which is secreted in extremely low amounts (if at all) by the gonads, has a five- to tenfold higher affinity for the androgen receptor than does testosterone. Many androgen-sensitive tissues, such as the prostate and skin, have the enzymatic machinery to convert the androgen precursors secreted by the adrenals into testosterone and DHT [6]. This process, whereby androgen precursors are converted to DHT in the same cells in which DHT exerts its action, without release of intermediate steroids into the circulation, has been called intracrinology [7]. This mechanism, which involves various steroidogenic enzymes such as steroid sulfatase, type 1 3β-hydroxysteroid dehydrogenase (3β-HSD), type 5 17β-HSD and, finally, 5α-reductase (types 1 and 2), ensures maximum conversion of testosterone into DHT (Figure 1).

There is also good evidence that the DHT formed in peripheral tissues is essentially metabolized locally before its appearance in the circulation [8,9]. Phase I DHT catabolites might include androstanedione, androsterone (ADT), epiandrosterone, androstane-3α,17β-diol (3α-DIOL) and androstane-3β,17β-diol, which are formed by the action of a series of 3α/β-HSD and 17β-HSD isoforms (Figure 1) [10–13]. However, most if not all of the androgen target tissues synthesize HSD isoforms that are capable of back converting the phase I metabolites into DHT, suggesting that fine regulation of these enzymes is extremely important, in addition to the serum levels of circulating precursors, for the concentrations of DHT in androgen target tissues [13]. For many years, phase I DHT metabolites, which have no significant androgenic activity, were considered to be the end products of the androgenic signal. It was first believed that the amount of these metabolites in the circulation reflected the metabolism of androgens and that these 5α-reduced androgens would eventually be eliminated by the phase II conjugating enzymes found in the liver or kidney [14–16]. Indeed, Phase II catabolism, through glucuronidation and sulfation by the liver and/or the kidneys, is the well accepted pathway for the complete inactivation and elimination of exogenous compounds, such as drugs and pollutants.

Urinary 3α-DIOL glucuronide (3α-DIOLG) was first isolated by Mauvais-Jarvis and Baulieu after intravenous administration of radioactive testosterone to humans [17].

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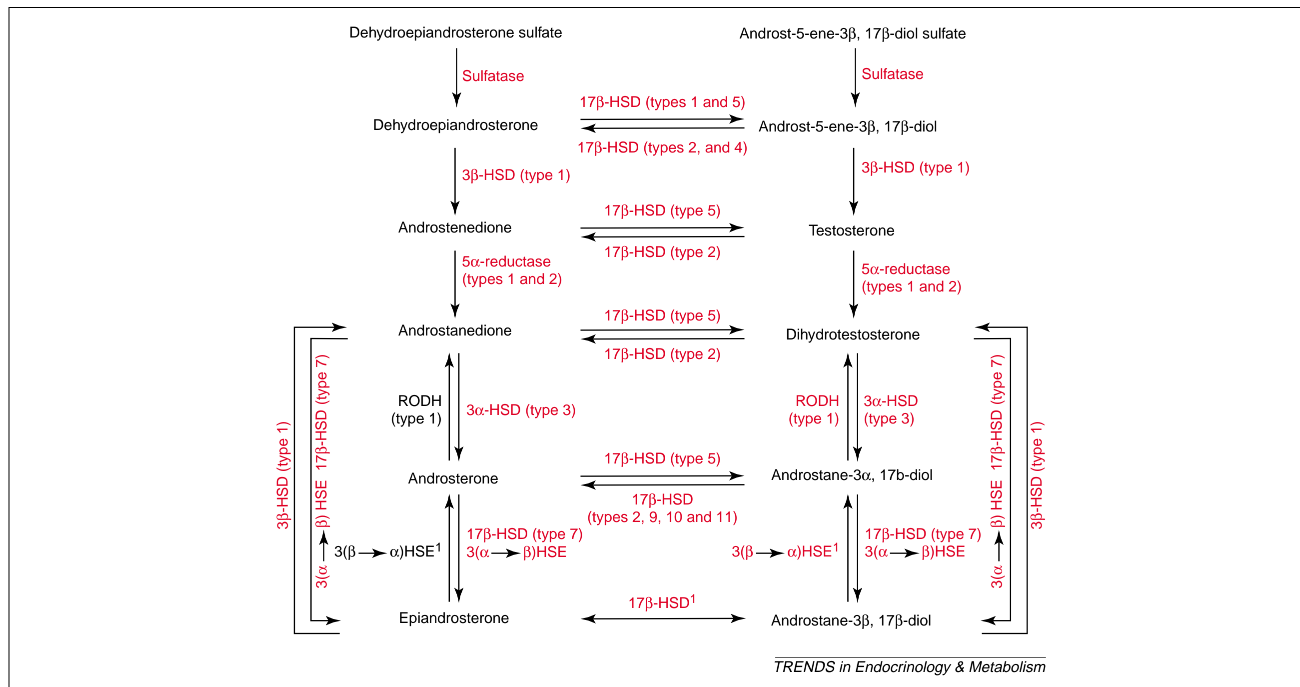

Figure 1. Enzymes involved in metabolism of androgens in peripheral intracrine tissues [6,10–13]. Dehydroepiandrosterone, its sulfate, androst-5-ene-3β,17β-diol and its sulfate, and androstenedione are secreted by the adrenals, whereas testosterone is produced by the testes. Abbreviations: HSD, hydroxy steroid dehydrogenase; HSE, hydroxysteroid epimerase; RODH, retinoldehydrogenase; 1, the enzyme has not been isolated so far.

This group subsequently showed that the production of 3α-DIOLG was higher in men than that in women and, in addition, that the transformation of testosterone to 3α-DIOLG was lower in individuals with the testicular feminization syndrome [18]. Finally, it was also found that the amount of urinary 3α-DIOLG was higher when testosterone was administered topically rather than intravenously [19]. These data strongly suggest that extrahepatic tissues contribute to the production of urinary 3α-DIOLG. In addition, the formation of 3α-DIOLG by the skin both *in vivo* and *in vitro* was demonstrated by several authors [19–21]. Further studies conducted by Horton's group also suggested that the levels of circulating 3α-DIOLG reflect androgen metabolism in androgen target tissues, such as the skin and prostate [8]. In 1986, it was reported that ADT glucuronide (ADTG) was present in the circulation at concentrations that were 20-fold higher than those of 3α-DIOLG, and that this 5α-reduced androgen glucuronide could also be an indicator of androgen metabolism in peripheral tissues [22].

In women, increased production of DHEAS, DHEA, 4-DIONE and/or testosterone by the adrenals and/or ovaries generally causes hirsutism and/or acne [23]. In this situation, circulating levels of 3α-DIOLG and ADTG are also much higher than those seen in normal women, whereas serum levels of the phase 1 DHT metabolites remain almost unchanged, supporting a major role for UDP-glucuronosyltransferase (UGT) enzymes in the *in situ* metabolism of DHT [24,25]. Serum levels of the conjugates are also increased after oral or topical administration of DHEA or 4-DIONE in the presence of no change or minimal change in the blood levels of non-conjugated androgen metabolites [26]. These observations support the concept that 5α-reduced androgen glucuronides found in the circulation are produced *in situ* in peripheral tissues after conversion of the adrenal and/or gonadal steroid precursors first into DHT and, subsequently, into phase I DHT metabolites, without release of these intermediate steroid precursors and metabolites into the circulation [6,9]. Consequently, the glucuronidation of phase I metabolites by UGT enzymes in androgen-sensitive tissues should be considered as the end of the androgenic signal. In the circulation, two major phase II DHT metabolites, 3α-DIOLG and ADTG, have been identified, but low amounts of DHTG and 3β-DIOLG were also detected [1,24,27].

UGT enzymes

Conjugation of compounds, including steroids, by glucuronidation has been demonstrated in all vertebrates studied to date. This reaction, which corresponds to the transfer of the glucuronosyl group from UDP-glucuronic acid to small hydrophobic molecules, is catalyzed by enzymes of the UGT superfamily. The resulting glucuronide products are more polar, generally water soluble, less toxic and more easily excreted from the body than is the parent compound. More than 45 different UGT cDNA clones have been isolated from seven mammalian species, including 18 human UGT clones [28,29]. Based upon homology of primary structures, the UGT proteins have been categorized into two families, UGT1 and UGT2, with UGT2 being subdivided into two subfamilies, UGT2A and UGT2B (Figure 2). Members of the UGT1 family share $>50\%$ identity with each other, but $<50\%$ identity with members of the UGT2 family.

In humans, UGT1A enzymes are all encoded by a complex gene comprising 17 exons localized on chromosome 2q37;

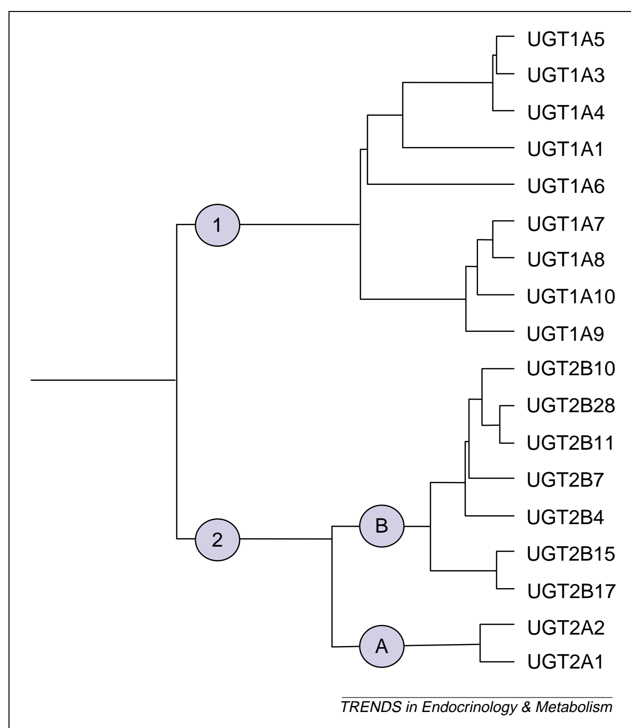

Figure 2. Phylogenetic tree of the 18 human UDP-glucuronosyltransferases (UGTs). The UGT proteins have been categorized into two families, UGT1 and UGT2, with UGT2 being subdivided into two subfamilies, UGT2A and UGT2B. Amino acid sequences of human UGT1A and UGT2B enzymes were from the GenBank database. *UGT1A2, UGT1A11, UGT1A12* and *UGT1A13* are pseudogenes. The human UGT2B enzymes isolated to date are named according to their chronological order of isolation. Five human *UGT2B* pseudogenes have also been isolated, whereas 16 UGT2B enzymes have been characterized in rats, monkeys and rabbits.

the different isoforms are generated by alternative splicing at 13 different sites in exon 1 in combination with the four common exons 2–5 [30]. Nine functional proteins and four pseudogenes have been identified from the *UGT1A* gene. Six enzymes of the UGT1A family are synthesized in the liver (UGT1A1, A3, A4, A5, A6 and A9), whereas the three remaining isoforms (UGT1A7, A8 and A10) are synthesized in the gastrointestinal tract [31]. It is thought that these three UGTs serve as a first line of metabolic defense for many synthetic substances and pollutants that enter the body. The specificity of the UGT1A isoforms has been investigated for both exogenous and endogenous substrates, such as bilirubin, for which glucuronidation is an essential metabolic pathway for its elimination and detoxification [30]. Several polymorphisms identified in exon 1 or in the promoter region of the *UGT1A1* gene have definitively identified the role of this isoform for bilirubin conjugation, because these genetic variations are all associated with the hyperbilirubinemia observed in Criggler–Najjar and Gilbert syndromes [32]. Interestingly, members of the UGT1A family also conjugate estradiol and estrone (UGT1A1) and the catecholestrogens, 2-hydroxyestrone and 4-hydroxyestrone (UGT1A3 and UGT1A9, respectively) [33,34]. Of the nine UGT1A members, only UGT1A4 conjugates 3α-DIOL and ADT, but with a low efficiency [35]. This is not surprising, because the specificity of UGT1A isoforms is mainly towards phenol compounds such as 4-nitrophenol, flavanoids and anthraquinones.

In contrast to the UGT1A family, each UGT2 subfamily member is encoded by a separate gene composed of six exons [36]. The two members of the UGT2A subfamily (UGT2A1 and UGT2A2) are restricted to the olfactory system and conjugate several classes of odorant molecules [31]. These UGT2A isoforms might protect the body from aerial exogenous substances and contribute to the termination of the olfactory stimulus.

However, enzymes of the UGT2B subfamily are synthesized in a wide range of tissues throughout the body. The human *UGT2B* genes are clustered on chromosome 4q13–21.1 and encode seven functional proteins; five pseudogenes have also been identified [36]. The functional human UGT2B enzymes isolated to date are UGT2B4, B7, B10, B11, B15, B17 and B28, which were named according to their chronological order of isolation [29]. The isoform UGT2B4 mainly conjugates bile and fatty acids, whereas UGT2B10 and B11 are specific for fatty acids, namely the eicosanoid metabolites [37]. UGT2B28, which is only synthesized in the liver and mammary gland, conjugates estradiol and 3α-DIOL, although its capacity to conjugate 3α-DIOL is much lower than that of UGT2B7, B15 and B17 [29]. In fact, these three UGT2Bs have a remarkably high capacity to conjugate androgens and here we focus on these isoforms, which are currently thought to be the major enzymes responsible for conjugating androgens in the human body.

UGT2B7

The *UGT2B7* gene has only recently been characterized [38], although the isolation of its two polymorphic forms (UGT2B7 H268 and Y268) was reported almost ten years ago [39]. *UGT2B7* transcripts have been detected with the use of RT–PCR in the intestine, liver, kidney, skin, brain, uterus and mammary glands [40]. However, this enzyme is not present in the prostate and adipose tissue. UGT2B7 is known particularly for its wide spectrum of specificity for all classes of steroids. Indeed, this isoform has a high capacity for conjugating 5α-reduced metabolites of mineralocorticoids, glucocorticoids, progestins and androgens [41]. UGT2B7 also efficiently conjugates 5β-reduced C21 and C19 steroids, indicating that UGT2B7 might contribute significantly to eliminating these phase I steroid metabolites from the liver. Interestingly, this enzyme also glucuronidates catecholestrogens, particularly 4-hydroxyestrone, a major metabolite of estradiol, which was identified as a powerful carcinogenic derivative of estrogens in breast and uterine tissues. Gestl *et al.* recently found that levels of UGT2B7 are particularly low in cancerous mammary gland tissue compared with those seen in normal tissue [42]. These authors suggest that UGT2B7 protects the mammary gland from the genetoxic 4-hydroxyestrone.

UGT2B7 conjugates the 3-hydroxy position of 3α-DIOL but not the 17-hydroxy position (Figure 3). ADT is a consistently good substrate for UGT2B7, whereas DHT, which has only a hydroxyl group at the 17-position, is a poor substrate for UGT2B7. The glucuronidation efficiency of UGT2B7 is almost tenfold higher for 3α-DIOL than for

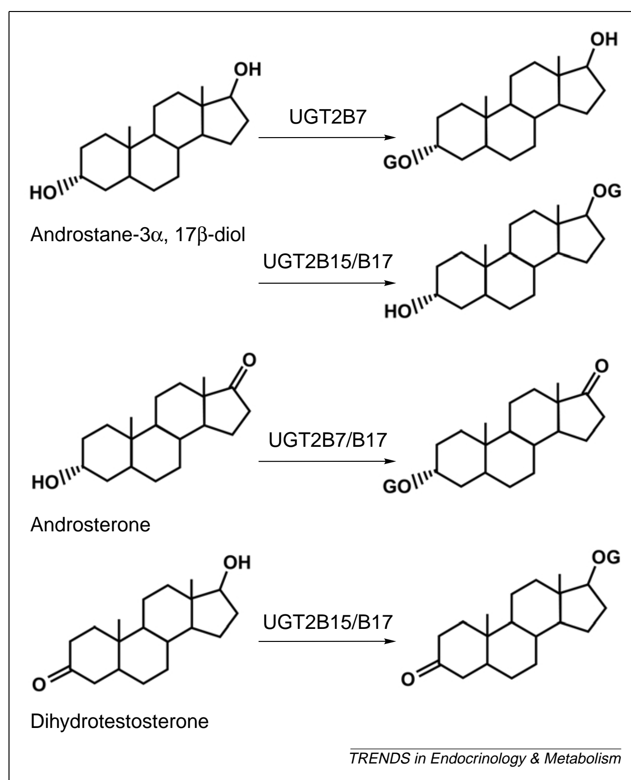

Figure 3. Specificity of UGT2B7, B15 and B17 for dihydrotestosterone, androstane-3α,17β-diol and androsterone. The steroid substrate was incubated with a microsomal preparation of the specified stably expressed UGT enzyme in the HK293 cell line and the conjugated steroid formed was identified by high performance liquid chromatography mass spectrometry [37,40]. UGT2B7 was found to conjugate androstane-3α,17β-diol at the 3-hydroxy position only, whereas UGT2B15 and UGT2B17 conjugated this compound at the 17-hydroxy position. Diglucuronides of androstane-3α,17β-diol were not detected. Androsterone was conjugated by UGT2B7 and UGT2B17, and dihydrotestosterone by UGT2B15 and UGT2B17.

ADT [40]. In androgen-sensitive tissues, such as skin and breast, UGT2B7 probably contributes to the conjugation of phase 1 DHT metabolites, particularly 3α-DIOL and, to a lower extent, ADT. Serum 3α-DIOLG concentrations in adult women are ≈2.5 nMol l^{-1}, whereas in men, they are fivefold higher. Interestingly, 3α-DIOL-17G is the predominant isomer (≈80%) found in the circulation in both sexes, indicating that UGT2B7 contributes to a relatively small proportion of 3α-DIOLG in the circulation, and that other UGT2Bs are involved in 3α-DIOLG production [43].

UGT2B15

A single nucleotide polymorphism has been described in the *UGT2B15* gene, which encodes UGT2B15, namely UGT2B15 D85 or UGT2B15 Y85 [44,45]. *UGT2B15* is expressed in the liver, kidney, skin, mammary gland and uterus but, in contrast to UGT2B7, this isoform is also found in the prostate. Of the three androgen-conjugating UGT2B enzymes, UGT2B15 is also unique because of its presence in adipose tissue [45]. Interestingly, the metabolic clearance rate of the exogenous product oxazepam, which is specifically conjugated by UGT2B15, is significantly higher in obese individuals than in non-obese controls, suggesting that UGT2B15 in extrahepatic tissues influences the inactivation and elimination of drug substances in the body [46]. In addition, Tchernoff *et al.* found that circulating 3α-DIOLG levels were significantly higher in obese patients than in controls [47].

UGT2B15 specifically conjugates the 17-hydroxy position of 5α-reduced androgens (Figure 3). This isoform has a high and moderate capacity for 3α-DIOL and DHT glucuronidation, respectively [40]. Its specificity for estrogens is limited to the catecholestrogens, 4-hydroxyestrone and 2-hydroxyestrone, which are glucuronidated with a much lower efficiency than is seen for 3α-DIOL. Although the two polymorphic forms have the same specificity, they differ significantly in their ability to conjugate DHT and 3α-DIOL, with UGT2B15 Y85 being twice as efficient as UGT2B15 D85 [45].

UGT2B17

UGT2B17 cDNA was isolated from a prostate cDNA library in 1996 and its transcripts were also detected in the liver and kidney, in addition to several androgen-sensitive tissues, such as skin, brain, mammary gland and uterus [48]. No polymorphisms have been found in UGT2B17 to date. The amino acid sequence homology between UGT2B15 and UGT2B17 is remarkably high (96%), but its specificity for 5α-reduced androgens is quite different. In contrast to UGT2B15, which is specific for the conjugation of the 17-hydroxy position of androgens, UGT2B17 glucuronidates both the 3-hydroxy position and the 17-hydroxy position [48].

The efficiency of UGT2B17 to conjugate 3α-DIOL is in the range reported for UGT2B15 and UGT2B7, whereas UGT2B17 has the highest capacity for ADT and DHT. Surprisingly, incubation of 3α-DIOL with stably transfected HK293 cells engineered to express *UGT2B17* results in the exclusive formation of 3α-DIOL-17G (Figure 3). These data indicate a major difference in the specificity of UGT2B17 and UGT2B7 for 3α-DIOL; UGT2B7 only conjugates 3α-DIOL at the 3-hydroxy position. Because its capacity to conjugate ADT is almost four times higher than that of UGT2B7, UGT2B17 is also thought to be the major ADT-conjugating enzyme. Interestingly, the concentrations of circulating ADTG are approximately five- to tenfold higher than those of 3α-DIOLG in both sexes [22].

UGT2B enzymes in the human prostate

The alveoli of the human prostate are composed of two cell types. The basal cells are small cells lining the periphery of the alveoli, whereas the luminal cells are large columnar cells in contact with the alveolar lumen. The two cell types play distinct roles in androgen formation and action (Figure 4). Type 1 3β-HSD, type 5 17β-HSD and types 1 and 2 5α-reductase are found in the basal cells, whereas in the luminal cells, where the androgen receptor is found exclusively, 5α-reductase predominates [49,50]. After castration, DHT concentrations in the prostate are reduced by almost 60%, indicating that testosterone precursors, such as DHEA, are responsible for a significant proportion of DHT in the prostate [51]. It is reasonable to suggest that DHT is formed locally in luminal cells from testosterone, which is provided by the circulation and/or metabolism of circulating adrenal steroid precursors (DHEA and 4-DIONE) in basal cells. Enzymes of phase I

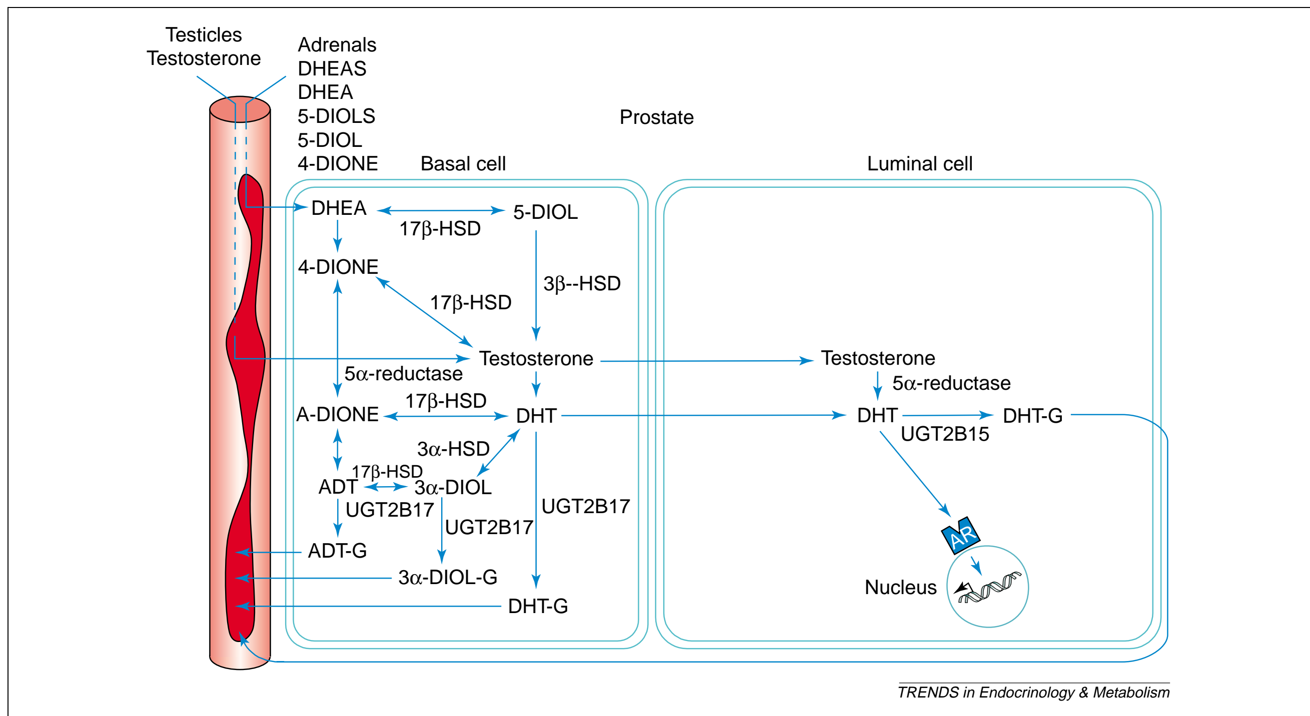

Figure 4. Androgen metabolism and inactivation by UDP-glucuronosyltransferases in the human prostate. Testosterone is secreted by the testes, whereas the adrenals produce DHEAS, DHEA, 5-DIOLS, 5-DIOL and 4-DIONE. Abbreviations: ADT, androsterone; 3α-DIOL, androstane-3α,17β-diol; ADT-G, androsterone glucuronide; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; DHT, dihydrotestosterone; 3α-DIOL-G, androstane-3α,17β-diol glucuronide; DHT-G, dihydrotestosterone glucuronide; 5-DIOL, androst-5-ene-3β,17β-diol; 5-DIOLS, androst-5-ene-3β,17β-diol sulfate; 4-DIONE, androstenedione; A-DIONE, androstanedione; 3β-HSD, 3β-hydroxysteroid dehydrogenase, 4–5-isomerase; 17β-HSD, 17β-hydroxysteroid dehydrogenase; 3α-HSD, 3α-hydroxysteroid dehydrogenase; UGT, UDP-glucuronosyltransferase.

DHT catabolism are also present in basal cells, but they are not detected in luminal cells, which form the largest part of the human prostate [10,52,53]. This absence of phase I catabolic enzymes from luminal cells favors high concentrations of DHT. Indeed, DHT concentrations in the prostate are almost ten times higher than those of testosterone and phase I DHT metabolites [51,54].

In 1978, Chung and Coffey demonstrated the glucuronidation of DHT by a prostate tissue homogenate [55]. To support the presence of conjugating activity in this tissue, large concentrations of 3α-DIOLG and ADTG were also reported [54]. Finally, the expression of *UGT2B15* and *UGT2B17* was subsequently established in the prostate [40]. As illustrated in Figure 5, the UGT2B17 protein is detected in basal cells, whereas UGT2B15 is only found in luminal cells [56]. It is probable that 3α-DIOL and ADT formed in basal cells are easily converted to glucuronides by UGT2B17, whereas the action of UGT2B15 would be limited to DHT in the luminal cells. Taking into account the low levels of UGT2B15 protein found in the prostate, this situation favors high concentrations of DHT in this tissue, in agreement with previous biochemical observations on the intraprostatic levels of DHT. In addition, because the affinity of DHT for the androgen receptor is ~1000 times higher than that for UGT2B15, it is thought that UGT2B15 might conjugate only a fraction of the accumulated DHT formed in the luminal cells.

UGT2B15 and prostate cancer

Androgens play a determining role in prostate differentiation and development, and stimulate the growth of prostate cancer cells, thus indicating that changes in androgen concentrations might be associated with the risk for developing prostate cancer. The co-localization of the activating testosterone 5α-reductase enzyme, the androgen receptor and UGT2B15 enables the fine tuning of intracellular DHT concentrations and action. Because two polymorphic forms of UGT2B15 exist with different efficacies for DHT conjugation, it was reasonable to postulate that the presence of the low-conjugating allele *UGT2B15*D85* has an effect on DHT concentrations [45]. Two groups have recently conducted epidemiological studies to determine the potential role of the *UGT2B15* gene in prostate cancer risk. The first study was performed with 64 pathologically confirmed prostate cancers and 64 controls recruited in the Arkansas area [57]. The *UGT2B15*D85* allele was significantly more prevalent in prostate cancer patients (40.6%) than in controls (18.8%), and the risk of developing cancer in homozygous patients with the *UGT2B15*D85* allele was threefold higher. However, in the second study conducted on 380 Caucasians from Austria, including 190 patients with prostate cancer and 190 patients suffering from benign prostate hyperplasia, no association could be shown between the two alleles and prostate cancer [58]. It is clear that further studies are required for a better understanding of the role of *UGT2B15* polymorphism in prostate cancer development.

UGT2B enzymes in the human skin

Androgens are required in the skin for sexual hair and sebaceous gland development, and disorders of the

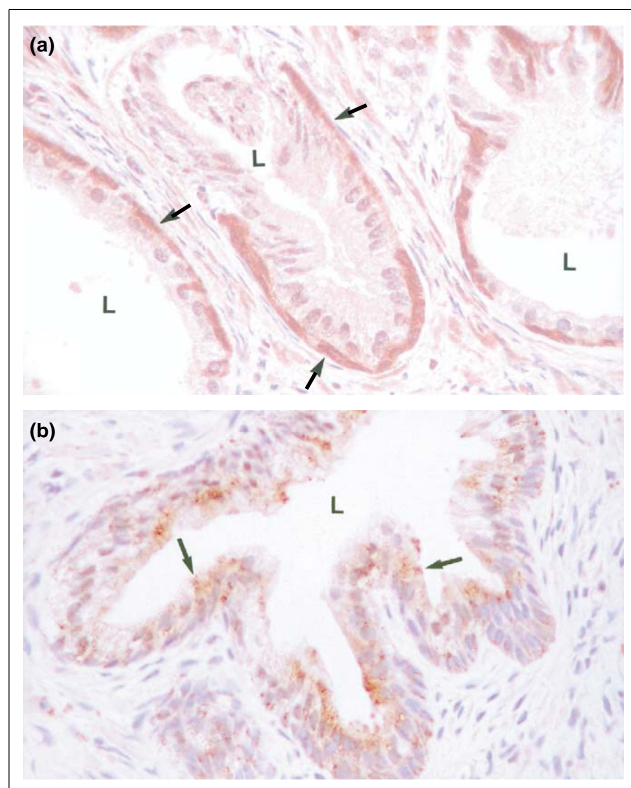

Figure 5. Immunohistochemical localization of **(a)** UGT2B17 and **(b)** UGT2B15 in human prostate. Immunostaining for UGT2B17 was exclusively detected in the basal epithelial cells of the alveoli (arrowheads), whereas staining for UGT2B15 was found in the epithelial luminal cells (arrows). L indicates the alveolar lumen;. Abbreviation: UGT, UDP-glucuronosyltransferase.

pilosebaceous unit, namely hirsutism, acne vulgaris and pattern alopecia, are androgen dependent [59–61]. For instance, hirsutism in women is generally characterized by increased androgen production from the ovaries and/or adrenal glands and/or enhanced sensitivity of the skin to circulating androgens. Skin contains all the steroidogenic enzymes responsible for the conversion of DHEAS to DHT, along with phase I DHT catabolic enzymes and phase II UGT2B7, B15 and B17 [23,40]. Although several studies have reported that circulating 3α-DIOLG and ADTG concentrations are good markers of the changes in androgen metabolism that occur in hirsutism, acne and alopecia, it is still not clear whether these blood levels reflect local alterations of androgen metabolism that might cause accumulation of DHT in the tissue or simply result from the overproduction of androgen precursors by the classical steroidogenic tissues generally seen in these disorders [23,62]. One of the difficulties in using these blood markers for evaluating the pathogenesis of skin disorders is the simultaneous presence of UGT2B7, B15 and B17 in this tissue [40]. In addition, 3α-DIOLG and ADTG in blood originate from several androgen-sensitive tissues and the contribution of each can vary. For a better understanding of the role of UGT2B enzymes in association with steroidogenic enzymes implicated both in DHT formation and phase I DHT metabolism in the skin, it would be useful to localize with precision the UGT2B enzymes, and to determine their levels of expression both in normal tissue and in tissue from patients with various skin disorders.

Conclusions

Although DHT is converted to inactive phase I metabolites in androgen-sensitive tissues, the steroidogenic enzymes involved in back formation of these metabolites into DHT are also present in several tissues. The specificity and tissue distribution of androgen-conjugating UGT2B enzymes indicate that these enzymes are involved locally in androgen metabolism, which leads to complete inactivation of the phase I androgen metabolites. It is thought that the addition of a polar group to the parent molecule, which is catalyzed by the UGT2B enzymes, represents the end of the androgenic signal. Because recent data have shown that these UGT2Bs can be modulated by several factors, including the androgens themselves and growth factors, the inactivating enzymes probably play an essential role in controlling androgen concentrations in androgen-sensitive tissues [63–65].

References

1 Bélanger, A. *et al.* (1994) Changes in serum concentration of conjugates and unconjugated steroids in 40- to 80-year old men. *J. Clin. Endocrinol. Metab.* 79, 1086–1090
2 Couzinet, B. *et al.* (2001) The postmenopausal ovary is not a major androgen-producing gland. *J. Clin. Endocrinol. Metab.* 86, 5060–5066
3 Korth-Schutz, S. *et al.* (1976) Serum androgens in normal prepubertal and pubertal children and in children with precocious adrenarche. *J. Clin. Endocrinol. Metab.* 42, 117–124
4 Hornsby, P.J. (2002) Aging of the human adrenal cortex. *Ageing Res. Rev.* 1, 229–242
5 Zhou, Z.X. *et al.* (1995) Specificity of ligand-dependent androgen receptor stabilization: receptor domain interactions influence ligand dissociation and receptor stability. *Mol. Endocrinol.* 9, 208–218
6 Labrie, F. *et al.* (2003) Endocrine and intracrine sources of androgens in women: inhibition of breast cancer and other roles of androgens and their precursor dehydroepiandrosterone. *Endocr. Rev.* 24, 152–182
7 Labrie, F. (1991) Intracrinology. *Mol. Cell. Endocrinol.* 78, C113–C118
8 Horton, R. and Lobo, R. (1986) Peripheral androgens and the role of androstanediol glucuronide. *Clin. Endocrinol. Metab.* 15, 293–306
9 Horton, R. (1992) Dihydrotestosterone is a peripheral paracrine hormone. *J. Androl.* 13, 23–27
10 Dufort, I. *et al.* (2001) Human types 1 and 3 3α-hydroxysteroid dehydrogenases: differential lability and tissue distribution. *J. Clin. Endocrinol. Metab.* 86, 841–846
11 Labrie, F. *et al.* (2000) Role of 17 β-hydroxysteroid dehydrogenases in sex steroid formation in peripheral intracrine tissues. *Trends Endocrinol. Metab.* 11, 421–427
12 Luu-The, V. (2001) Analysis and characteristics of multiple types of human 17β-hydroxysteroid dehydrogenase. *J. Steroid Biochem. Mol. Biol.* 76, 143–151
13 Andersson, S. (2001) Steroidogenic enzymes in skin. *Eur. J. Dermatol.* 11, 293–295
14 Giagulli, V.A. *et al.* (1991) Is plasma 5α-androstane 3α,17β-diol glucuronide a biochemical marker of hirsutism in women? *J. Steroid Biochem. Mol. Biol.* 39, 55–61
15 Giagulli, V.A. *et al.* (1993) Origin and significance of plasma androsterone glucuronide levels: a parameter of adrenal androgen secretion and hepatic 5α-reductase activity. *J. Clin. Endocrinol. Metab.* 76, 918–923
16 Deslypere, J.P. *et al.* (1982) Plasma 5 α-androstane-3 α,17 β-diol and urinary 5 α-androstane-3 α,17 β-diol glucuronide, parameters of peripheral androgen action: a comparative study. *J. Clin. Endocrinol. Metab.* 54, 386–391
17 Mauvais-Jarvis, P. and Baulieu, E.E. (1965) Studies on testosterone metabolism. IV. Urinary 5α- and β-androstanediols and testosterone glucuronide from testosterone and dehydrolsoandrosterone sulfate in

normal people and hirsute women. *J. Clin. Endocrinol. Metab.* 25, 1167–1178

18 Mauvais-Jarvis, P. *et al.* (1970) Studies on testosterone metabolism in subjects with testicular feminization syndrome. *J. Clin. Invest.* 49, 31–40

19 Mauvais-Jarvis, P. *et al.* (1969) *In vivo* studies on testosterone metabolism by skin of normal males and patients with the syndrome of testicular feminization. *J. Clin. Endocrinol. Metab.* 29, 417–421

20 Lobo, R.A. *et al.* (1987) Production of 3 α-androstanediol glucuronide in human genital skin. *J. Clin. Endocrinol. Metab.* 65, 711–714

21 Pasupuleti, V. *et al.* (1988) Conversion of dihydrotestosterone to androstanediol glucuronide by female sexual skin. *Steroids* 51, 269–282

22 Bélanger, A. *et al.* (1986) Levels of plasma steroid glucuronides in intact and castrated men with prostatic cancer. *J. Clin. Endocrinol. Metab.* 62, 812–815

23 Chen, W. *et al.* (2002) Cutaneous androgen metabolism: basic research and clinical perspectives. *J. Invest. Dermatol.* 119, 992–1007

24 Brochu, M. *et al.* (1987) Plasma levels of C-19 steroids and 5 α-reduced steroid glucuronides in hyperandrogenic and idiopathic hirsute women. *Fertil. Steril.* 48, 948–953

25 Lobo, R.A. *et al.* (1983) Evidence for the importance of peripheral tissue events in the development of hirsutism in polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* 57, 393–397

26 Labrie, F. *et al.* (1997) Physiological changes in dehydroepiandrosterone are not reflected by serum levels of active androgens and estrogens but of their metabolites: intracrinology. *J. Clin. Endocrinol. Metab.* 82, 2403–2409

27 Whorwood, C.B. *et al.* (1992) Plasma levels of C19 steroid glucuronides in pre-menopausal women with non-classical congenital adrenal hyperplasia. *J. Steroid Biochem. Mol. Biol.* 42, 211–221

28 Mackenzie, P.I. *et al.* (1997) The UDP glycosyltransferase gene superfamily: recommended nomenclature update based on evolutionary divergence. *Pharmacogenetics* 7, 255–269

29 Lévesque, E. *et al.* (2001) Isolation and characterization of the *UGT2B28* cDNA encoding a novel human steroid conjugating UDP-glucuronosyltransferase. *Biochemistry* 40, 3869–3881

30 Owens, I.S. *et al.* (1996) The novel UGT1 gene complex link bilirubin, xenobiotics, and therapeutic drug metabolism by encoding UDP-glucuronosyltransferases isoenzymes with a common carboxyl terminus. *J. Pharmacokinet. Biopharm.* 24, 491–508

31 Tukey, R.H. and Strassburg, C.P. (2001) Genetic multiplicity of the human UDP-glucuronosyltransferases and regulation in the gastrointestinal tract. *Mol. Pharmacol.* 59, 405–414

32 Burchell, B. (2003) Genetic variation of human UDP-glucuronosyltransferase: implications in disease and drug glucuronidation. *Am. J. Pharmacogenomics* 3, 37–52

33 Albert, C. *et al.* (1999) The monkey and human uridine diphosphate-glucuronosyltransferase UGT1A9, expressed in steroid target tissues, are estrogen conjugating enzymes. *Endocrinology* 140, 3292–3302

34 Cheng, Z. *et al.* (1998) Glucuronidation of catechol estrogens by expressed human UDP-glucuronosyltransferases (UGTs) 1A1, 1A3, and 2B7. *Toxicol. Sci.* 45, 52–57

35 Green, M.D. and Tephly, T.R. (1996) Glucuronidation of amines and hydroxylated xenobiotics and endobiotics catalyzed by expressed human UGT1.4 protein. *Drug. Metab. Dispos.* 24, 356–363

36 Turgeon, D. *et al.* (2000) Isolation and characterization of the human *UGT2B15* gene, localized within a cluster of UGT2B genes and pseudogenes on chromosome 4. *J. Mol. Biol.* 295, 489–504

37 Turgeon, D. *et al.* (2003) Glucuronidation of arachidonic and linoleic acid metabolites by human UDP-glucuronosyltransferases. *J. Lipid Res.* 44, 1182–1191

38 Carrier, J-S. *et al.* (2000) Isolation and characterization of the human *UGT2B7* gene. *Biochem. Biophys. Res. Commun.* 272, 616–621

39 Ritter, J.K. *et al.* (1990) Cloning and expression of human liver UDP-glucuronosyltransferase in COS-1 cells: 3,4-catechol estrogens and estriol as primary substrates. *J. Biol. Chem.* 265, 7900–7906

40 Turgeon, D. *et al.* (2001) Relative enzymatic activity, protein stability and tissue distribution of human steroid metabolizing UGT2B subfamily members. *Endocrinology* 142, 778–787

41 Girard, C. *et al.* (2003) Human UDP-glucuronosyltransferase: UGT2B7 conjugates mineralocorticoid and glucocorticoid metabolites. *Endocrinology* 144, 2659–2688

42 Gestl, S.A. *et al.* (2002) Expression of UGT2B7, a UDP-glucuronosyltransferase implicated in the metabolism of 4-hydroxyestrone and all-*trans* retinoic acid, in normal human breast parenchyma and in invasive and *in situ* breast cancers. *Am. J. Pathol.* 160, 1467–1479

43 Rittmaster, R.S. *et al.* (1988) Androstanediol glucuronide isomers in normal men and women and in men infused with labeled dihydrotestosterone. *J. Clin. Endocrinol. Metab.* 66, 212–216

44 Chen, F. *et al.* (1993) Characterization of a cloned human dihydrotestosterone/androstanediol UDP-glucuronosyltransferase and its comparison to other steroid isoforms. *Biochemistry* 32, 10648–10657

45 Lévesque, É. *et al.* (1997) Isolation and characterization of UGT2B15(Y85): a UDP-glucuronosyltransferase encoded by a polymorphic gene. *Pharmacogenetics* 7, 317–325

46 Court, M.H. *et al.* (2002) Stereoselective conjugation of oxazepam by human UDP-glucuronosyltransferases (UGTs): S-oxazepam is glucuronidated by UGT2B15, while R-oxazepam is glucuronidated by UGT2B7 and UGT1A9. *Drug Metab. Dispos.* 30, 1257–1265

47 Tchernof, A. *et al.* (1999) Expression of the androgen metabolizing enzyme *UGT2B15* in adipose tissue and relative expression measurement using a competitive RT–PCR method. *Clin. Endocrinol. (Oxf.)* 50, 637–642

48 Beaulieu, M. *et al.* (1996) Isolation and characterization of a novel cDNA encoding a human UDP-glucuronosyltransferase active on C19 steroids. *J. Biol. Chem.* 271, 22855–22862

49 Pelletier, G. *et al.* (2001) Immunoelectron microscopic localization of 3β-hydroxysteroid dehydrogenase and type 5 17β-hydroxysteroid dehydrogenase in the human prostate and mammary gland. *J. Mol. Endocrinol.* 26, 11–19

50 Pelletier, G. *et al.* (1998) Localization by *in situ* hybridization of steroid 5 α-reductase isozyme gene expression in the human prostate and preputial skin. *J. Urol.* 160, 577–582

51 Bélanger, B. *et al.* (1989) Comparison of residual C-19 steroids in plasma and prostatic tissue of human, rat and guinea pig after castration: unique importance of extratesticular androgens in men. *J. Steroid Biochem.* 32, 695–698

52 Huang, X.F. and Luu-The, V. (2001) Characterization of the oxidative 3α-hydroxysteroid dehydrogenase activity of human recombinant 11-cis-retinol dehydrogenase. *Biochim. Biophys. Acta* 1547, 351–358

53 Huang, X.F. and Luu-The, V. (2000) Molecular characterization of a first human 3(α → β)-hydroxysteroid epimerase. *J. Biol. Chem.* 275, 29452–29457

54 Bélanger, A. *et al.* (1990) Determination of non-conjugated and conjugated steroid levels in plasma and prostate after separation on C-18 columns. *Ann. N. Y. Acad. Sci.* 595, 251–259

55 Chung, L.W. and Coffey, D.S. (1978) Androgen glucuronide. II. Differences in its formation by human normal and benign hyperplastic prostates. *Invest. Urol.* 15, 385–388

56 Barbier, O. *et al.* (2000) Cellular localization of uridine diphosphoglucuronosyltransferase 2B enzymes in the human prostate by *in situ* hybridization and immunohistochemistry. *J. Clin. Endocrinol. Metab.* 85, 4819–4826

57 McLeod, S.L. *et al.* (2000) An allele-specific polymerase chain reaction method for the determination of the D85Y polymorphism in the human UDP-glucuronosyltransferase *2B15* gene in a case–control study of prostate cancer. *Ann. Surg. Oncol.* 7, 777–782

58 Gsur, A. *et al.* (2002) A polymorphism in the UDP-glucuronosyltransferase *2B15* gene (D85Y) is not associated with prostate cancer risk. *Cancer Epidemiol. Biomarkers Prev.* 11, 497–498

59 Labrie, F. *et al.* (2000) Intracrinology and the skin. *Horm. Res.* 54, 218–229

60 Zouboulis, C.C. (2000) Human skin: an independent peripheral endocrine organ. *Horm. Res.* 54, 230–242

61 Deplewski, D. and Rosenfield, R.L. (2000) Role of hormones in pilosebaceous unit development. *Endocr. Rev.* 21, 363–392

62 Azziz, R. *et al.* (2000) Idiopathic hirsutism. *Endocr. Rev.* 21, 347–362

63 Guillemette, C. *et al.* (1997) Differential regulation of two UDP-glucuronosyltransferases, UGT2B15 and UGT2B17, in human prostate LNCaP cells. *Endocrinology* 138, 2998–3005

64 Lévesque, É. *et al.* (1998) Effect of interleukins on UGT2B15 and UGT2B17 steroid uridine diphosphate-glucuronosyltransferase expression and activity in the LNCAP cell line. *Endocrinology* 139, 2375–2381

65 Lévesque, É. *et al.* (1998) Effect of fibroblastic growth factors (FGF) on steroid UDP-glucuronosyltransferase expression and activity in the LNCaP cell line. *J. Steroid Biochem. Mol. Biol.* 64, 43–48