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Review Article

Alternative androgen pathways

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Abstract

Steroidogenic routes to androgens have been discovered and characterized over the last two decades that fall outside the Δ^4 and Δ^5 "classical androgen pathways" to testosterone and 5α-dihydrotestosterone. There has been considerable investigation into these routes that has come with natural inconsistencies and overlap in naming that can make it difficult to discover information about them as might be needed in a clinical context. This expository review uses "alternative androgen pathways" to include what has been called the "backdoor" pathway to 5α-dihydrotestosterone, the 5α-dione pathway and pathways to 11-oxygenated steroids. A brief history of what led to the discovery of these pathways, basic information about the steroids and proteins involved in their biosynthesis as well as a summary of clinically significant findings is provided. PubChem CIDs for all steroids have been compiled to help authors avoid naming errors in their work. Modest suggestions for future work in these pathways are also given at the end. Patient comprehension and the clinical diagnosis of relevant conditions such as hyperandrogenism can be impaired by the lack of clear and consistent knowledge of alternative androgen pathways; the authors hope this review will accurately disseminate such knowledge to facilitate the beneficial treatment of such patients.

Introduction

The classical androgen pathway is composed of the steroidogenic adrenal and gonadal metabolic pathways that transform cholesterol to the androgen testosterone (T), which is then transformed into the potent androgen 5α-dihydrotestosterone (DHT). Broadly, androgens are understood to exert their primary effects through binding to cytosolic androgen receptor (AR) that is translocated to the nucleus upon androgen binding and ultimately results in the transcriptional regulation of a number of genes via Androgen Responsive Elements.[1] This androgen response mechanism is perhaps best known and characterized in the context of male sexual differentiation and puberty, but plays a role in a variety of tissue types and processes.[2]

In 2003, a "backdoor" androgen pathway to DHT that did not proceed through T was discovered in the tammar wallaby.[3] Shortly after this study, the pathway was further characterized, and its potential clinical relevance in conditions involving androgen biosynthesis in humans was proposed.[4] In the years following, other distinct pathways to potent 11-oxygenated androgens have been characterized and also been described as "backdoor".[5]

The relatively recent characterization of these "alternative androgen pathways" in the literature can confound the search for clinical information in cases where androgen steroidogenesis is relevant. In addition to the reuse of the term "backdoor", studies across different androgen pathways have also used different names for the same molecules. While such naming inconsistencies are notoriously common when it comes to biomolecules,[6] instances of incorrect names

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are easy to find and are almost certainly attributable to complex naming rules for organic molecules. In addition, pathway definitions can sometimes differ in the precise initial/terminal molecules, and the inclusion/exclusion of such points can hinder queries in electronic pathway databases.

Alternative androgen pathways are now known to be responsible for the production of biologically active androgens in humans, and there is growing evidence that they play a role in clinical conditions associated with hyperandrogenism. Understanding androgen steroidogenesis at the level of detail presented in this paper and establishing consensus names and pathway specifications would facilitate access to information towards diagnosis and patient comprehension.

History

Backdoor Pathways to 5α-Dihydrotestosterone

In 1987, Eckstein et al.[7] incubated rat testicular microsomes in the presence of radiolabelled steroids and demonstrated that 5α-androstane-3α,17β-diol is preferentially produced from 17α-hydroxyprogesterone (17OHP). While "androstanediol" was used to denote both 5α-androstane-3α,17β-diol and 5α-androstane-3β,17β-diol, "3α-diol" is used here to abbreviate 5α-androstane-3α,17β-diol in this paper as it is a common convention and emphasizes it as the 3α-reduced derivative of DHT. The function of 3α-diol was not known at that time.

Tammar wallaby pouch young do not show sexually dimorphic circulating levels of T and DHT during prostate development which suggested that another androgenization mechanism was responsible. In 2000, Shaw et al.[8] demonstrated that circulating 3α-diol mediates prostate development in these pouch young via conversion to DHT in target tissues. While 3α-diol's AR binding affinity is five orders of magnitude lower than DHT (generally described as AR inactive), it was known 3α-diol can be oxidized back to DHT via the action of a number of dehydrogenases.[9]

In 2003, Wilson et al.[3] incubated the testes of tammar wallaby pouch young with radiolabelled progesterone to show that 5α-reductase expression in this tissue enabled a novel pathway from 17OHP to 3α-diol without T as an intermediate. The sequence of this transformation along steroids is shown below (the full names can be found in § Abbreviations and Identifiers as well as #Figure 2):

- 17OHP → 17OHDHP → 5α-Pdiol → AST → 3α-diol

In 2004, Mahendroo et al.[10] demonstrated that an overlapping novel pathway is operating in mouse testes, generalizing what had been demonstrated in tammar wallaby:

- P4 → 5α-DHP → AlloP5→ 5α-Pdiol → AST → 3α-diol

The term "backdoor pathway" was coined by Auchus in 2004[4] and defined as a route to DHT that: 1) bypasses conventional intermediates androstenedione (A4) and T; 2) involves 5α-reduction of 21-carbon (C_{21}) pregnanes to 19-carbon (C_{19}) androstanes; and 3) involves the 3α-oxidation of 3α-diol to DHT. The backdoor pathway explained how androgens are produced under certain normal and pathological conditions in humans when the classical androgen pathway cannot fully explain the observed consequences. The pathway Auchus defined adds DHT to the terminus of the pathway described by Wilson et al. in 2003:

- 17OHP → 17OHDHP → 5α-Pdiol → AST → 3α-diol → DHT

The clinical relevance of these results was demonstrated in 2012 for the first time when Kamrath et al.[11] attributed the urinary metabolites to the androgen backdoor pathway from 17OHP to DHT in patients with steroid 21-hydroxylase (encoded by the gene CYP21A2) enzyme deficiency.

5α-Dione Pathway

In 2011, Chang et al.[12] demonstrated that an alternative pathway to DHT was dominant and possibly essential in castration-resistant prostate cancer (CRPC) by presenting evidence from cell culture and xenograft models:

- A4 → 5α-dione → DHT

While this pathway was described as the "5α-dione pathway" in a 2012 review,[13] the existence of such a pathway in the prostate was hypothesized in a 2008 review by Luu-The et al.[14]

A modern outlook of the synthesis of the backdoor pathways to DHT and the 5α-dione pathway is shown in #Figure 2.

11-Oxygenated Androgen Pathways

11-Oxygenated androgens are the products of a distinct alternative androgen pathway. The 11-oxygenated C_{19} steroids 11β-hydroxyandrostenedione (11OHA4) and 11-ketoandrostenedione (11KA4) were known since the 1950s to be products of the human adrenal but were understood as androgen inactive in humans. Their role as substrates to potent androgens had been overlooked in humans until recently, though they were long known in teleost fishes.[15]

Rege et al. in 2013[16] measured 11-oxygenated androgen levels in healthy women and showed that both 11-ketodihydrotestosterone (11KT) and 11β-hydroxytestosterone (11OHT) could activate the AR.

In 2013, Storbeck et al.[17] demonstrated the existence of 11-oxygenated androgen pathways in androgen-dependent prostate cancer cell culture. The authors demonstrated that A4 transformed to 11OHA4 in the adrenal can ultimately be converted into 11KT and 11-ketodihydrotestosterone (11KDHT) as shown in #Figure 3. The authors found that 11KT activity is comparable to that of T, and 11-ketodihydrotestosterone (11KDHT) activity is comparable to that of DHT, while the activities of 11OHT and 5α-dihydro-11β-hydroxytestosterone (11OHDHT) were observed to be about half of T and DHT, respectively. However, androgen activity in that study was only assessed at a single concentration of 1 nM.[17] Full dose responses for 11KT and 11KDHT were characterized in a study by Pretorius et al. in 2016[18] that showed 11KT and 11KDHT both bind and activate the AR with affinities, potencies, and efficacies that are similar to that of T and DHT, respectively.

Barnard et al.[5] in 2017 demonstrated metabolic pathways from C_{21} steroids to 11KDHT that bypasses A4 and T *in vitro* in a prostate cancer derived cell line, an aspect that is similar to that of the backdoor pathway to DHT. These newly discovered pathways to 11-oxygenated androgens were also described as "backdoor" pathways due to this similarity, and were further characterized in subsequent studies.[19][20]

A diagram of the 11-oxygenated androgen pathways is shown in #Figure 3.

Definition

The term "alternative androgen pathway" is used in this paper to refer to any pathway that produces potent androgens without a T intermediate. This subsumes all three groups of androgen pathways described in the previous section. A new term that describes the three groups of pathways (as well as future discoveries) will allow a single entry point into scientific information when alternatives to the classical androgen pathway[21][22] must be considered.

Nomenclature and Background

The complex naming rules of organic chemistry have resulted in the use of incorrect steroid names in published studies. Many examples of errors in systematic names can be found via Google Scholar[23][24] for molecules described in

this paper, motivating this expository section on steroid nomenclature to facilitate the use of correct names.

Almost all biologically relevant steroids can be presented as a derivative of a parent hydrocarbon structure that serves as a skeleton.[25] These parent structures have specific names, such as pregnane, androstane, etc. The derivatives carry various functional groups called suffixes or prefixes after the respective numbers indicating their position in the steroid nucleus.[26] The widely-used trivial steroid names such as progesterone, testosterone or cortisol can also be used as base names to derive new names, however, by adding prefixes only rather than suffixes e.g., the steroid 17α-hydroxyprogesterone has a hydroxy group (-OH) at position 17 of the steroid nucleus comparing to progesterone. The letters α and β[27] denote absolute stereochemistry at chiral centers (a specific nomenclature distinct from the R/S convention[28] of organic chemistry). In steroids drawn from the standard perspective used in this paper, α-bonds are depicted on figures as dashed wedges and β-bonds as solid wedges.

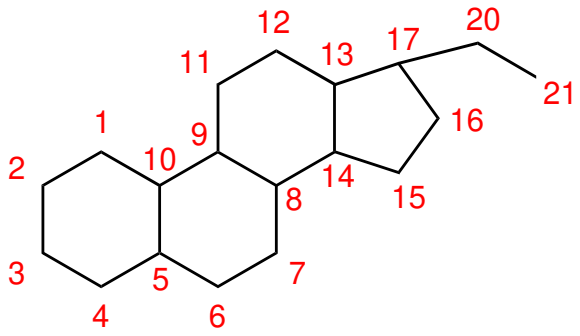

Figure 1 Numbering of carbon atoms up to position 21 (positions 18 and 19 are omitted) in a hypoth etical steroid nucleus, as defined by the Nomenclature of Steroids.

The molecule "11-deoxycortisol" is an example of a derived name that uses cortisol as a parent structure without an oxygen atom (hence "deoxy") attached to position 11 (as a part of a hydroxy group).[29] The numbering of positions of carbon atoms in the steroid nucleus is set in a template found in the Nomenclature of Steroids[30] that is used regardless of whether an atom is present in the steroid in question. Although the nomenclature defines more than 30 positions, this review only needs numbering for the first 21 (#Figure 1).

Unsaturated carbons (generally, ones that are a part of a double bond) in the steroid nucleus are indicated by changing -ane to -ene.[31] This change was traditionally done in the parent name, adding a prefix to denote the position, with or without Δ (Greek capital delta) which designates unsaturation, for example, 4-pregnene-11β,17α-diol-3,20-dione (also Δ^4-pregnene-11β,17α-diol-3,20-dione) or 4-androstene-3,11,17-trione (also Δ^4-androstene-3,11,17-trione). However, the Nomenclature of Steroids recommends the locant of a double bond to be always adjacent to the syllable designating the unsaturation, therefore, having it as a suffix rather than a prefix, and without the use of the Δ character, i.e. pregn-4-ene-11β,17α-diol-3,20-dione or androst-4-ene-3,11,17-trione. The double bond is designated by the lower-numbered carbon atom, i.e. "Δ^4-" or "4-ene" means the double bond between positions 4 and 5. The saturation of carbons of a parent steroid can be done by adding "34dihydro-" prefix,[32] i.e. saturation of carbons 4 and 5 of testosterone with two hydrogens is 4,5α-dihydrotestosterone or 4,5β-dihydrotestosterone. Generally, when there is no ambiguity, one number of a hydrogen position from a steroid with a saturated bond may be omitted, leaving only the position of the second hydrogen atom, e.g., 5α-dihydrotestosterone or 5β-dihydrotestosterone. The Δ^5-steroids are those with a double bond between carbons 5 and 6 (#Figure 1) and the Δ^4 steroids are those with a double bond between carbons 4 and 5.[33][31] The classical androgen pathway is generally described in terms of a sequence of Δ^5 compounds:

- P5 → 17OHP5 → DHEA→ A5

and Δ^4 compounds:

- P4 → 17OHP → AlloP5→ A4 → T

The abbreviations like "P4" and "A4" refer to Δ^4-steroids, while "P5" and "A5" refer to Δ^5-steroids.

The suffix -ol denotes a hydroxy group, while the suffix -one denotes an oxo group. When two or three identical groups are attached to the base structure at different positions, the suffix is indicated as -diol or -triol for hydroxy, and -dione or -trione for oxo groups, respectively. For example, 5α-pregnane-3α,17α-diol-20-one has a hydrogen atom at the 5α position (hence the "5α-" prefix), two hydroxy groups (-OH) at the 3α and 17α positions (hence "3α,17α-diol" suffix) and an oxo group (=O) at the position 20 (hence the "20-one" suffix). However, erroneous use of suffixes can be found, e.g., "5α-pregnan-17α-diol-3,11,20-trione"[23] [*sic*] — since it has just one hydroxy group (at 17α) rather than two, then the suffix should be -ol, rather than -diol, so that the correct name to be "5α-pregnan-17α-ol-3,11,20-trione".

According to the rule set in the Nomenclature of Steroids, the terminal "e" in the parent structure name should be elided before the vowel (the presence or absence of a number does not affect such elision).[26] This means, for instance, that if the suffix immediately appended to the parent structure name begins with a vowel, the trailing "e" is removed from that name. An example of such removal is "5α-pregnan-17α-ol-3,20-dione", where the last
textquotedble" of "pregnane" is dropped due to the vowel "o") at the beginning of the suffix -ol. Some authors incorrectly use this rule, eliding the terminal "e" where it should be kept, or vice versa.[24]

The term "11-oxygenated" refers to the presence of an oxygen atom as an oxo (=O) or hydroxy (-OH) substituent at carbon 11. "Oxygenated" is consistently used within the chemistry of the steroids[34] since the 1950s.[35] Some studies use the term "11-oxyandrogens"[36][37] as an abbreviation for 11-oxygenated androgens, to emphasize that they all have an oxygen atom attached to carbon at position 11.[38][39] However, in chemical nomenclature, the prefix "oxy" is associated with ether functional groups, i.e., a compound with an oxygen atom connected to two alkyl or aryl groups (R-O-R),[40] therefore, using "oxy" within the name of a steroid class may be misleading. One can find clear examples of "oxygenated" to refer to a broad class of organic molecules containing a variety of oxygen containing functional groups in other domains of organic chemistry,[41] and it is appropriate to use this convention here.

Even though "keto" is a standard prefix in organic chemistry, the 1989 recommendations of the Joint Commission on Biochemical Nomenclature discourage the application of the prefix "keto" for steroid names, and favor the prefix "oxo" (e.g., 11-oxo steroids rather than 11-keto steroids), because "keto" includes the carbon that is part of the steroid nucleus and the same carbon atom should not be specified twice.[42]

Biochemistry

A more detailed description of each alternative androgen pathway introduced in § History is provided below. Proteins are described by their Human Genome Organisation Gene Nomenclature Committee (HGNC) gene symbols[43][44], i.e. the symbols of the genes that they are encoded by (e.g., 5α-reductases type 1 is abbreviated by SRD5A1). Full enzyme/protein names are not shown in the text since the steroid names that are being used are already unwieldy, but they can be found in § Abbreviations and Identifiers.

Backdoor Pathways to 5α-Dihydrotestosterone

While 5α-reduction is the last transformation in the classical androgen pathway, it is the first step in the backdoor pathways to 5α-dihydrotestosterone that acts on either 17OHP or P4 which are ultimately converted to DHT.

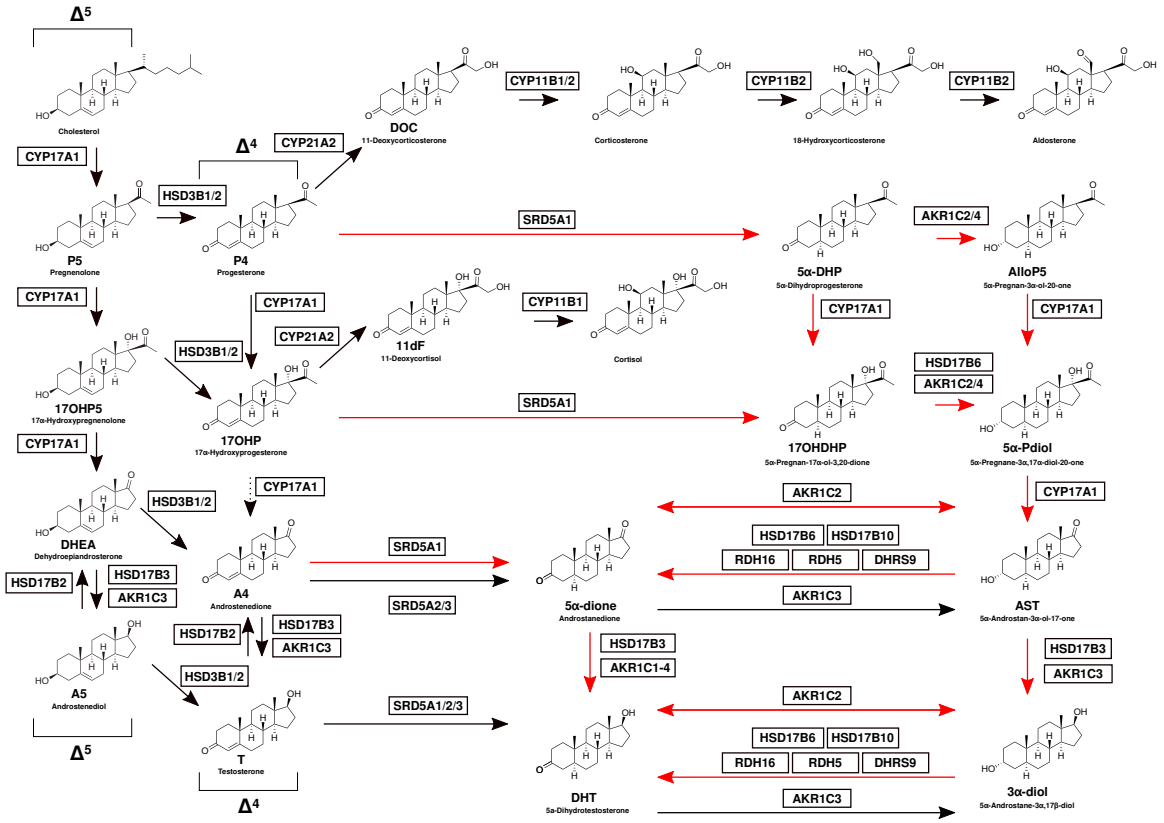

Figure 2 The androgen backdoor pathways from 17α-hydroxyprogesterone or progesterone towards 5α-dihydrotestosterone roundabout testosterone and androstenedione (red arrows), as well as the 5α-dione pathway that starts with 5α-reduction of androstenedione, embedded within classical androgen pathway (black arrows). Transformation arrows are annotated with the HGNC symbol (boxed text) of the gene for the enzyme that catalyzes the transformation. Some additional proteins that are required for specific transformations including steroidogenic acute regulatory protein (STAR), cytochromes b_5 (CYB5A), cytochrome P450 reductase (POR) are not shown for clarity. Only negligible A4 is produced from 17OHP,[45] denoted as a dotted arrow.

17α-Hydroxyprogesterone Pathway

The first step of this pathway is the 5α-reduction of 17OHP to 5α-pregnan-17α-ol-3,20-dione (17OHDHP, since it is also known as 17α-hydroxy-dihydroprogesterone). The reaction is catalyzed by SRD5A1.[46][47] 17OHDHP is then converted to 5α-pregnane-3α,17α-diol-20-one (5α-Pdiol) via 3α-reduction by a 3α-hydroxysteroid dehydrogenase isozyme (AKR1C2 and AKR1C4)[21][48] or HSD17B6, that also has 3α-reduction activity.[49][50] 5α-Pdiol is also known as 17α-hydroxyallopregnanolone or 17OH-allopregnanolone. 5α-Pdiol is then converted to 5α-androstan-3α-ol-17-one (AST) by 17,20-lyase activity of CYP17A1 which cleaves a side-chain (C17-C20 bond) from the steroid nucleus, converting a C_{21} steroid (a pregnane) to C_{19} steroid (an androstane or androgen). AST is 17β-reduced to 5α-androstane-3α,17β-diol (3α-diol) by HSD17B3 or AKR1C3.[22] The final step is 3α-oxidation of 3α-diol in target tissues to DHT by an enzyme that has 3α-hydroxysteroid oxidase activity, such as AKR1C2,[51] HSD17B6, HSD17B10, RDH16, RDH5, and DHRS9.[47] This oxidation is not required in the classical androgen pathway.

The pathway can be summarized as:

- 17OHP → 17OHDHP → 5α-Pdiol → AST → 3α-diol → DHT

Progesterone Pathway

The pathway from P4 to DHT is similar to that described above from 17OHP to DHT, but the initial substrate for 5α-reductase here is P4 rather than 17OHP. Placental P4 in the male fetus is the feedstock for the backdoor pathway found operating in multiple non-gonadal tissues.[21]

The first step in this pathway is 5α-reduction of P4 towards 5α-dihydroprogesterone (5α-DHP) by SRD5A1. 5α-DHP is then converted to allopregnanolone (AlloP5) via 3α-reduction by AKR1C2 or AKR1C4. AlloP5 is then converted to 5α-Pdiol by the 17α-hydroxylase activity of CYP17A1. This metabolic pathway proceeds analogously to DHT as the 17α-hydroxyprogesterone pathway described the previous subsection.

The pathway can be summarized as:

- P4 → 5α-DHP → AlloP5 → 5α-Pdiol → AST → 3α-diol → DHT

5α-Dione Pathway

5α-reduction is also the initial transformation of the 5α-dione pathway where A4 is converted to androstanedione (5α-dione) by SRD5A1 and then directly to DHT by either HSD17B3 or AKR1C3. While this pathway is unlikely to be of biological relevance in healthy humans, it has been found operating in castration-resistant prostate cancer.[12]

5α-dione can also be transformed into AST, which can then either be converted back to 5α-dione or be transformed into DHT along the common part of the backdoor pathways to DHT (i.e., via 3α-diol).[12][52]

This pathway can be summarized as:

- A4 → 5α-dione → DHT

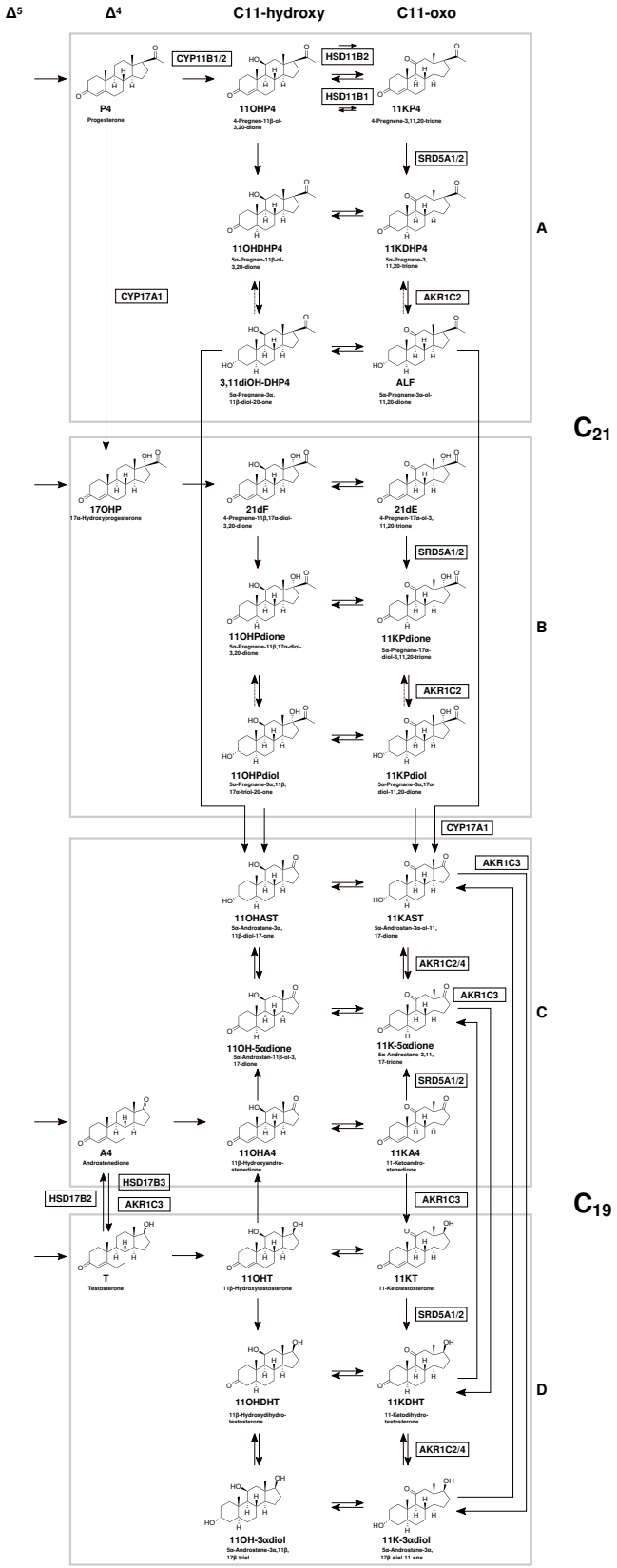

Figure 3 Abbreviated routes to 11-oxygenated androgens with transformations (black arrow) annotated with the HGNC symbol (boxed text) of the gene for the enzyme that catalyzes the transformation. The four groups of steroids are distinguished by the C17 substituent configuration associated with four distinct precursors, A: the conversion of progesterone B: the conversion of 17-hydroxyprogesterone by CYP11B1, SRD5A, and AKR1C2 in the C11-hydroxy and -oxo C_{21} steroids C: the conversion of androstenedione D: the conversion of testosterone by CYP11B1, HSD11B, SRD5A, AKR1C3 and AKR1C2/4 in the C11-hydroxy and -oxo C_{19} steroids. CYP17A1 catalyzes the C_{21} steroids to C_{19} steroids. Some transformations which are presumed to exist but not yet shown to exist are depicted with dotted arrows. Some CYP17A1 mediated reactions that transform 11-oxygenated androgens classes (grey box) are omitted for clarity. Δ^5 compounds that are transformed to Δ^4 compounds are also omitted for clarity.

11-Oxygenated Androgen Pathways

There are two known 11-oxygenated androgens that are both C_{19}: 11KT and 11KDHT. Some work[53][54][55] suggests that though 11OHT and 11OHDT may not have significant androgenic activity as they were once thought to possess, they may still be important precursors to androgenic molecules. The relative importance of the androgens depends on their activity, circulating levels and stability.

Routes to 11-oxygenated androgens (#Figure 3) also fall under our definition of alternative androgen pathways. These routes begin with four Δ^4 steroid entry points (P4, 17OHP, A4 and T) and can then proceed through a set of transformation sequences that can be organized in a lattice-like structure. The reachability a particular steroid in the lattice depends on the expression of a given enzyme in the tissue where that steroid is synthesized or transported to, which in turn can depend on the health status of the individual. All the steroid products in this lattice have a hydroxy group or an oxo group covalently bound to the carbon atom at position 11 (#Figure 1).

The steroids 11OHA4 and 11KA4 have been established as having minimal androgen activity,[16][17][56] but remain important molecules in this context since they act as androgen precursors.

The complex lattice structure seen in #Figure 3 can be understood broadly as four Δ^4 steroid entry points that can undergo a common sequence of three transformations:

1. 11β-hydroxylation by CYP11B1 in the adrenal cortex,
2. 5α-reduction by SRD5A1/2,
3. reversible 3α-reduction/oxidation of the ketone/alcohol by AKR1C2 or AKR1C4.

These steroids correspond to the "C11-hydroxy" column in #Figure 3. This sequence is replicated in the parallel column of "C11-oxo" steroids, in which are a result of 11β-oxidation of the alcohol to a ketone.[17] HSD11B1 catalyzes both oxidation of the 11OH substrates and reduction of the 11K substrates, while HSD11B2 only catalyzes the oxidation. It should be noted that while 11β-hydroxylation by CYP11B2 has been shown *in vitro*, this isozyme is only known to be expressed in the zona glomerulosa of the adrenal cortex which would be unlikely to encounter the Δ^4 substrates.

There are additional transformations in the lattice that cross the derivatives of the entry points. AKR1C3 catalyzes (reversibly in some cases) 17β-reduction of the ketone to transform between 17-oxo and 17β-OH steroids. Pregnanes can also be transformed to 17-oxo steroids via CYP17A1 17α-hydroxylase activity. Some 17α-OH pregnanes can be transformed into 17-oxo steroids via 17,20 lyase activity of CYP17A1.

There are many possible routes to androgens as seen in #Figure 3, but only three are known in healthy humans. A4 is synthesized in the adrenal where it can undergo 11β-hydroxylation to yield 11OHA4,[57][58][59] an important circulating androgen precursor, which is further transformed to 11KA4 and then 11KT (primarily outside the adrenal in peripheral tissue):

- A4 → 11OHA4 → 11KA4 → 11KT

This route is regarded as the primary 11-oxygenated androgen pathway in healthy humans. It is thought that the T entry point also operates in normal human physiology, but much less that A4:

- T → 11OHT → 11OHA4 → 11KA4 → 11KT
- T → 11OHT → 11KT

The diminished role of these pathways is supported by that fact that the adrenal produces significantly more 11OHA4 than OHT.[16][60]

Other Backdoor Androgen Pathways

There is currently no good evidence for androgens from the C_{21} steroid entry points (P4,

17OHP) operating in healthy humans. These entry points are relevant in the clinical context, as discussed in the next section.

There is one report of 5α-androstane-3β,17β-diol (3β-diol) as a precursor to DHT[61] through a backdoor pathway, but this does not yet seem widely accepted in later reviews.[62]

Clinical Significance

11-Oxygenated Androgens

Characterizing serum concentration profiles of 11-oxygenated androgens in humans is technically challenging but essential for clinical applications. Just as with classical androgens, low concentrations, similarity of different androgens and cross-reactivity of molecules are just some of the barriers that must be mitigated to measure concentrations with sufficient accuracy for clinical utility. Circulating androgen levels do not always reflect tissue steroid concentrations as is evidenced by poor correlations between intra-tissue and blood levels. The analytic chemistry methods used to quantitate androgens can be technically difficult, and not all protocols have been validated to the same degree. In general, most published concentration profiles of 11-oxygenated androgens should be assumed to come with considerable uncertainty. While there is a long history to 11-oxygenated steroids in a number of diseases, there is no profile measurement that is considered a standard clinical tool.

Broadly, higher quality studies with better analytic methods that cover larger numbers of steroid types, careful disease subtyping etc. seem to be required before strong clinical applications can be expected.

A recent study[63] found 11KHDHT levels remained below the limit of detection (<20 pg/mL) and no commercial 11OHDHT standard was available to measure against. In the same study on samples drawn from a diverse pool of participants, serum 11KT levels were found to range between 197.63 pg/mL and 461.40 pg/mL, while 11OHT levels ranged between 87.34 pg/mL and 252.61 pg/mL. 11KT is thought to circulate at similar levels to T in healthy women.[64]

It may be that 11KT is the main androgen in women since it circulates at similar level to T and may[64] or may not[65][66] decline with age as T does. While 11KDHT is equipotent to DHT, circulating levels of 11KDHT are lower than DHT.

Unlike T and A4, 11-oxygenated androgens are not known to be aromatized to estrogens in the human body.[67][68] It is possible that 11-oxygenated estrogens may be produced in some pathological conditions such as feminizing adrenal carcinoma.[69]

Each condition in the following subsections has demonstrated potential roles for 11-oxygenated androgens. While there are no known C_{21} androgens (11-oxygenated or otherwise), they do arise as precursors to C19 androgens and some C21 steroid levels are thought to be associated with some of these conditions.

Hyperandrogenism

Alternative androgen pathways are not always considered in the clinical evaluation of patients with hyperandrogenism.[70] Hyperandrogenism may lead to presentations including congenital adrenal hyperplasia (CAH), other disorders of sex development (DSDs), polycystic ovary syndrome (PCOS), premature adrenarche and Cushing's disease.[71] Not considering alternative androgen pathways in clinical hyperandrogenism investigations may lead to misdiagnosis.[70]

Despite the prevailing notion that T and DHT are the primary human androgens, this notion only applies to healthy men.[72] Although T has been traditionally used as a biomarker of hyperandrogenism,[73] it correlates poorly with clinical measurements of androgen excess.[72] While T levels can appear normal, ignoring the alternative androgen pathways may lead

to diagnostic errors since hyperandrogenism may be caused by potent androgens such as DHT produced by a backdoor pathway and 11-oxygenated androgens.[74][75]

It had been suggested that 11OHA4 and its urinary metabolites could have clinical applications as biomarkers of hyperandrogenism in women.[76] Increased adrenal 11OHA4 production was characterized, using changes in A4:11OHA4 and 11β-hydroxyandrosterone:11β-hydroxyetiocholanolone ratios, in Cushing's disease,[77] hirsutism,[78] CAH and PCOS.[79] These ratios have still not been established as a standard clinical as a diagnostic tool.

Congenital Adrenal Hyperplasia

CAH refers to a group of autosomal recessive disorders characterized by impaired cortisol biosynthesis[80] caused by a deficiency in any of the enzymes required to produce cortisol in the adrenal.[81][82] This deficiency leads to an excessive accumulation of steroid precursors that are converted to androgens and lead to hyperandrogenism. "Classical CAH" is generally considered as a DSD since it can lead to virilization and cliteromegaly in females, but it is potentially fatal in either sex. The "non-classical" or "late onset" forms of CAH are non-fatal and generally present with more subtle symptoms. The potential contributions from alternative androgen pathways remain underappreciated in CAH.

In CAH due to deficiency of 21-hydroxylase[11] or cytochrome P450 oxidoreductase (POR),[47][83] the associated elevated 17OHP levels result in flux through the backdoor pathway to DHT that begins with 5α-reduction of 17OHP. This pathway may be activated regardless of age and sex.[84] Fetal excess of 17OHP in CAH may contribute to DHT synthesis that leads to external genital virilization in newborn girls with CAH.[47] P4 levels may also be elevated in CAH,[85][86] leading to androgen excess via the backdoor pathway from P4 to DHT.[87] 17OHP and P4 may also serve as substrates to 11-oxygenated androgens in CAH.[20]

Serum levels of the C_{21} 11-oxygenated steroids 11OHP4 and 21dF have been known to be elevated in (non-classical/classical) CAH since about 1990,[88][89] and LC-MS/MS profiles that include these steroids have been proposed for clinical applications.[90] Classical CAH patients receiving glucocorticoid therapy had C_{19} 11-oxygenated steroid serum levels that were elevated 3-4 fold compared to healthy controls.[91] In that same study, the levels of C_{19} 11-oxygenated androgens correlated positively with conventional androgens in women but negatively in men. The levels of 11KT were 4 times higher compared to that of T in women with the condition. In adult women with CAH, the ratio of DHT produced in a backdoor pathway to that produced in a conventional pathway increases as control of androgen excess by glucocorticoid therapy deteriorates.[92] In CAH patients with poor disease control, 11-oxygenated androgens remain elevated for longer than 17OHP, thus serving as a better biomarker for the effectiveness of the disease control.[93][94] In males with CAH, 11-oxygenated androgen levels may indicate the presence testicular adrenal rest tumors.[94][95]

Other Disorders of Sex Development

Both the classical and backdoor androgen pathway to DHT are required for normal human male genital development.[83][96] Deficiencies in the backdoor pathway to DHT from 17OHP or from P4[48][46] lead to underverilization of the male fetus,[97][98] as placental P4 is a precursor to DHT in the backdoor pathway.[21]

A case study[48] of five 46,XY (male) patients from two families demonstrated that atypical genital appearance were attributed to mutations in AKR1C2 and/or AKR1C4, which operate exclusively in the backdoor pathway to DHT. Mutations in the AKR1C3 and genes involved in the classical androgen pathway were excluded as the causes for the atypical appear-

ance. The 46,XX (female) relatives of affected patients, having the same mutations, were phenotypically normal and fertile. Although both AKR1C2 and AKR1C4 are needed for DHT synthesis in a backdoor pathway (#Figure 2), the study found that mutations in AKR1C2 only were sufficient for disruption.[48] However, these AKR1C2/AKR1C4 variants leading to DSD are rare and have been only so far reported in just those two families.[99] This case study emphasizes the role of AKR1C2/4 in the alternative androgen pathways.

Isolated 17,20-lyase deficiency syndrome due to variants in CYP17A1, cytochrome b_5, and POR may also disrupt the backdoor pathway to DHT, as the 17,20-lyase activity of CYP17A1 is required for both classical and backdoor androgen pathways. This rare deficiency can lead to DSD in both sexes, with affected girls being asymptomatic until puberty, when they show amenorrhea.[99]

11-oxygenated androgens may play important roles in DSDs.[100][101][47] 11-oxygenated androgen fetal biosynthesis may coincide with the key stages of production of cortisol — at weeks 8–9, 13–24, and from 31 and onwards. In these stages, impaired CYP17A1 and CYP21A2 activity lead to increased ACTH due to cortisol deficiency and the accumulation of substrates for CYP11B1 in pathways to 11-oxygenated androgens and could cause abnormal female fetal development.[100]

Polycystic Ovary Syndrome

PCOS is a heterogeneous and complex disorder that affects women's metabolism and fertility, and is poorly understood in terms of underlying causes. The diagnoses of PCOS that require hyperandrogenism tend to be associated with more severe disease phenotypes.[102] Both the ovary and the adrenal can be involved in the hyperandrogenism.

In PCOS, DHT may be produced in the backdoor androgen pathway from SRD5A1 activity.[103][104] Genes encoding enzymes required for the backdoor pathway to 5α-DHT (AKR1C2/4, SRD5A1/2, RDH16) are expressed at higher levels than normal in the theca cells of the PCOS ovary,[105] and could be responsible for hyperandrogenism.

There is a decades long history of research around the application C_{19} 11-oxygenated steroids (11OHA4, 11KA4, 11OHT and 11KT) as clinical disease markers.[39] Perhaps glibly summarizing this large body of work, there still seems to be a considerable lack of consensus as to which steroid profile might be useful in a clinical context. Some of the controversy can be attributed to the complex diagnostic framework around PCOS.

Premature Adrenarche

Although premature adrenarche has long been considered benign, the early appearance of pubic and/or axillary hair in girls (before 8 years of age) and boys (before 9 years of age) has been linked to several pathological risks, including cardiovascular risks and PCOS. The cause is unknown, but alternative androgen pathways have been implicated. Urinary metabolite analysis has been used to infer that there is increased 17,20-lyase activity of CYP17A1 and that it is likely that it leads to increased metabolic flux through the backdoor androgen pathway to DHT.[106] Another study observed 11KT/T ratios being higher in premature adrenarche girls (3.5 fold) vs. age-matched controls (2.5).[107] These findings may further understanding of the condition and associated risks.

Cushing's Disease

Cushing's disease itself characterized by cortisol excess, and patients commonly present with symptoms of hyperandrogenism, but these symptoms have not been correlated with serum androgen concentrations. A recent study [77] demonstrated that salivary concentration profiles of 11-oxygenated steroids, including 11OHA4 and 11KT, were elevated in untreated

Cushing's patients, and levels were reduced with treatment. The effect was strong enough for the study to claim that hyperandrogenism in Cushing's disease was caused by an excess of 11-oxygenated C_{19} steroids.

Prostate Cancer

High levels of 11KT, 11KDHT and 11OHDHT have also been detected in prostate cancer tissue [108] and there is some preliminary evidence that C_{19} 11-oxygenated steroids may play an important role at the stage of prostatic carcinogenesis. [109] At the time of writing, it can be difficult to summarize some of the conflicting claims about the relative abundance/importance of different steroids in prostate cancer.

Androgen deprivation is a therapeutic approach to prostate cancer that can be implemented by castration to eliminate gonadal T, but metastatic tumors may then develop into castration-resistant prostate cancer (CRPC). Although castration results in 90-95% decrease of serum T, DHT in the prostate is only decreased by 50%, supporting the notion that the prostate expresses necessary enzymes to produce DHT without testicular T.[14] The 5α-dione pathway was discovered in the context of CPRC (see § History), and is known to mitigate the effects of androgen deprivation therapy.

C_{19} 11-oxygenated androgens contribute significantly to the androgen pool[17][22] and play a previously overlooked role in the reactivation of androgen signaling in the CRPC patient. Serum 11KT levels are higher than any other androgen in 97% of CRPC patients, accounting for 60% of the total active androgen pool, and are not affected by castration.[110]

Benign Prostatic Hyperplasia, Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Androgens play a vital role in the development, growth and maintenance of the prostate. [14] The role of androgens has been considered not only in prostate cancer, but other prostate-related conditions such as BPH[14] and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).[111] Just as in prostate cancer, conflicting claims about the relative abundance/importance of different steroids demand resolution.

C_{21} 11-oxygenated steroids have been demonstrated as androgen precursors in BPH cell models (11OHP4 and 11KP4 to 11KDHT), BPH patient tissue biopsy and in their serum. [112]

Future Directions

The role of non-classical CAH in CP/CPPS

Relative steroid serum levels in CP/CPPS have suggested that CYP21A2 deficiency may play a role in the disease and that non-classical (mild) CAH due to CYP21A2 deficiency may be a comorbidity, even though non-classical CAH is generally thought to be asymptomatic in men. [113][114] Given the important role that androgens play in the health of the prostate, at least one study has hypothesized that CP/CPPS may be a consequence of a systemic condition as opposed to a localized condition of the prostate such as an infection, inflammation, or dysfunction.[111][115][116] Considering the potential roles that alternative androgen pathways play in the previously described disease areas, it seems that CP/CPPS would seem to be a good candidate to investigate the same way. The authors are not aware of any work that describes alternative androgen pathways in CP/CPPS.

The biomarkers of disease control in CAH due to CYP21A2 deficiency

Some studies suggested that in CAH patients with poor disease control, 11-oxygenated androgens remain elevated for longer than 17OHP, thus serving as a better biomarker for the effectiveness of the disease control than the

traditional indicator 17OHP.[93][94] It may be that 11OHP4 and 21dF, the substrates for 11-oxygenated androgens in pathologic conditions such as CAH rather than 11-oxygenated androgens themselves may serve as better biomarkers for the effectiveness of the disease control in CAH. 21dF has already been proposed as a better biomarker for CAH diagnosis than 17OHP,[117] but the role of 21dF and 11OHP4 as biomarkers of the effectiveness of the disease control in CAH remain to be studied.

SRD5A2 in the backdoor pathway to DHT

While the role of SRD5A1 in the backdoor pathway to DHT is established, it is not clear if SRD5A2 is involved.[11] Some authors [46][47] claim that the reduction of 17OHP to 17OHDHP by SRD5A1 is not "sufficient" or "efficient", as supported by measurements of rat SRD5A2 activity.[118] More recently, it has been shown that recombinant human SRD5A1 and SRD5A2 can catalyze the reduction of 17OHP at comparable rates to the reduction of P4.[5] Given both isozymes may be expressed in fetal tissues of both sexes,[119][120] the action of SRD5A2 in the backdoor pathway to DHT in humans may be worth more exploration.

Immune Response Regulation

Androgens are known to regulate the processes inside AR expressing immune cells and are assumed to play a role in sex differences in immune responses.[121][122][123] The roles of androgens in immune responses have been investigated in many clinical settings including the worldwide COVID-19 pandemic,[124][125] with enough investigation of anti-androgen therapy for meta-analysis.[126]

There seem to be relatively few reports on the links between alternative androgen pathways and the immune system though it has been shown that peripheral mononuclear blood cells produce 11KT from 11KA4 and that 11KT is the predominant androgen in that cell type.[127] Understanding what, if any, effects or therapeutic targets alternative androgen pathways offer in the context of immune processes may become an important research direction as the understanding of these pathways improves.

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Abbreviations and Identifiers

Steroids

Abbreviation	Systematic Name	Trivial Name[i]	Other Names and Abbreviations	PubChem CID
11dF	4-pregnene-17α,21-diol-3,20-dione	11-deoxycortisol	cortodoxone; 11-desoxycortisol; Reichstein's substance S	440707
11K-3αdiol	5α-androstane-3α,17β-diol-11-one			10125601
11K-5αdione	5α-androstane-3,11,17-trione	11-ketoandrostanedione	11-keto-5α-androstanedione	11185733

Abbreviation	Systematic Name	Trivial Name[h]	Other Names and Abbreviations	PubChem CID
11KA4	4-androstene-3,11,17-trione	11-ketoandrostenedione	androst-4-ene-3,11,17-trione; adrenosterone; Reichstein's substance G	223997
11KAST	5α-androstan-3α-ol-11,17-dione	11-ketoandrosterone		102029
11KDHP4	5α-pregnane-3,11,20-trione	11-ketodihydroprogesterone	allopregnanetrione	968899
11KDHT	5α-androstan-17β-ol-3,11-dione	11-ketodihydrotestosterone	5α-dihydro-11-keto testosterone; 5α-dihydro-11-keto-testosterone	11197479
11KP4	4-pregnene-3,11,20-trione	11-ketoprogesterone	pregn-4-ene-3,11,20-trione	94166
11KPdiol	5α-pregnane-3α,17α-diol-11,20-dione			92264183
11KPdione	5α-pregnan-17α-ol-3,11,20-trione			99568471
11KT	4-androsten-17β-ol-3,11-dione	11-ketotestosterone		5282365
11OH-3αdiol	5α-androstane-3α,11β,17β-triol			10286384
11OH-5αdione	5α-androstan-11β-ol-3,17-dione	11β-hydroxy-5α-androstanedione	adrenosterone-M	59087027
11OHA4	4-androsten-11β-ol-3,17-dione	11β-hydroxyandrostenedione	androst-4-en-11β-ol-3,17-dione	94141
11OHAST	5α-androstane-3α,11β-diol-17-one	11β-hydroxyandrosterone		10286365
11OHDHP4	5α-pregnan-11β-ol-3,20-dione	11β-hydroxydihydroprogesterone		11267580
11OHDHT	5α-androstane-11β,17β-diol-3-one	11β-hydroxydihydrotestosterone	5α-dihydro-11β-hydroxytestosterone; 11β,17β-dihydroxy-5α-androstan-3-one	10018051
11OHEt	5β-androstane-3α,11β-diol-17-one	11β-hydroxyetiocholanolone	3α,11β-dihydroxy-5β-androstan-17-one	101849
11OHP4	4-pregnen-11β-ol-3,20-dione	21-deoxycorticosterone	pregn-4-en-11β-ol-3,20-dione; 21-desoxycorticosterone; 11β-hydroxyprogesterone	101788
11OHPdiol	5α-pregnane-3α,11β,17α-triol-20-one			99601857
11OHPdione	5α-pregnane-11β,17α-diol-3,20-dione			99572627
11OHT	4-androstene-11β,17β-diol-3-one	11β-hydroxytestosterone		114920
17OHP5	5-pregnene-3β,17α-diol-20-one	17α-hydroxypregnenolone		91451
17OHDHP	5α-pregnan-17α-ol-3,20-dione	17α-hydroxydihydroprogesterone	5α-Pdione	11889565
17OHP	4-pregnen-17α-ol-3,20-dione	17α-hydroxyprogesterone		6238
21dE	4-pregnen-17α-ol-3,11,20-trione	21-deoxycortisone	pregn-4-en-17α-ol-3,11,20-trione; 21-desoxycortisone	102178
21dF	4-pregnene-11β,17α-diol-3,20-dione	21-deoxycortisol	1β,17α-dihydroxyprogesterone; pregn-4-ene-11β,17α-diol-3,20-dione; 21-desoxycortisol; 21-deoxyhydrocortisone	92827
3,11diOH-DHP4	5α-pregnane-3α,11β-diol-20-one	3α,11β-dihydroxy-5α-pregnan-20-one		10125849
3α-diol	5α-androstane-3α,17β-diol	5α-adiol; 3α-androstanediol		15818
3β-diol	5α-androstane-3β,17β-diol	3β-androstanediol		242332
5α-DHP	5α-pregnane-3,20-dione	5α-dihydroprogesterone		92810
5α-dione	5α-androstane-3,17-dione	androstanedione		222865
5α-Pdiol	5α-pregnane-3α,17α-diol-20-one	17α-hydroxyallopregnanolone		111243
A4	4-androstene-3,17-dione	androstenedione	androst-4-ene-3,17-dione	6128
A5	5-androstene-3β,17β-diol	androstenediol	androst-5-ene-3β,17β-diol	10634
A5-S	5-androstene-3β,17β-diol sulfate	androstenediol sulfate		13847309
ALDO	4-pregnene-11β,21-diol-3,18,20-trione	aldosterone		5839
ALF	5α-pregnan-3α-ol-11,20-dione	alfaxalone	alphaxalone; alphaxolone; 3α-hydroxy-5α-pregnane-11,20-dione	104845
AlloP5	5α-pregnan-3α-ol-20-one	allopregnanolone		92786
AST	5α-androstan-3α-ol-17-one	androsterone		5879

Abbreviation	Systematic Name	Trivial Name[1]	Other Names and Abbreviations	PubChem CID
CORT	4-Pregnene-11β,21-diol-3,20-dione	corticosterone	Kendall's compound B; Reichstein's substance H	5753
DHEA	5-androsten-3β-ol-17-one	dehydroepiandrosterone	3β-hydroxyandrost-5-en-17-one; androst-5-en-3β-ol-17-one	5881
DHEA-S	5-androsten-3β-ol-17-one sulfate	dehydroepiandrosterone sulfate		12594
DHT	5α-androstan-17β-ol-3-one	5α-dihydrotestosterone		10635
DOC	4-pregnen-21-ol,3,20-dione	11-deoxycorticosterone	desoxycorticosterone; 11-desoxycorticosterone; Reichstein's substance Q; desoxycortone	6166
F	4-pregnene-11β,17α,21-triol-3,20-dione	cortisol	hydrocortisone; Kendall's compound F; Reichstein's substance M	5754
P4	4-pregnen-3,20-dione	progesterone		5994
P5	5-pregnen-3β-ol-20-one	pregnenolone		8955
T	4-androsten-17β-ol-3-one	testosterone		6013

Note:

1. The steroids in this paper are referred to by their trivial names, as specified in the respective column. If a steroid has no conventional trivial name, then the systematic name is used for that purpose.

Enzymes

HGNC Gene Symbol	Enzyme Name
AKR1C2	aldo-keto reductase family 1 member C2; 3α-hydroxysteroid dehydrogenase type 3
AKR1C3	aldo-keto reductase family 1 member C3; 3α-hydroxysteroid dehydrogenase type 2; 17β-hydroxysteroid dehydrogenase type 5; HSD17B5
AKR1C4	aldo-keto reductase family 1 member C4; 3α-hydroxysteroid dehydrogenase type 1
CYP11A1	cytochrome P450 cholesterol side-chain cleavage enzyme; P450scc
CYP11B1	cytochrome P450 11β-hydroxylase; P450c11B1
CYP11B2	aldosterone synthase; P450c11B2
CYP17A1	cytochrome P450 17α-hydroxylase/17,20-lyase; P450c17
CYP21A2	cytochrome P450 21-hydroxylase; P450c21
DHRS9	dehydrogenase/reductase SDR family member 9; short-chain dehydrogenases/reductase 9
HSD11B1	11β-hydroxysteroid dehydrogenase type 1
HSD11B2	11β-hydroxysteroid dehydrogenase type 2
HSD17B3	17β-hydroxysteroid dehydrogenase type 3
HSD17B6	17β-hydroxysteroid dehydrogenase type 6; retinol dehydrogenase-like hydroxysteroid dehydrogenase; RL-HSD
HSD17B10	17β-hydroxysteroid dehydrogenase type 10
POR	cytochrome P450 oxidoreductase
RDH16	retinol dehydrogenase 16; RODH4
RDH5	retinol dehydrogenase 5

HGNC Gene Symbol	Enzyme Name
SRD5A1	steroid 5α-reductase type 1; 3-oxo-5α-steroid 4-dehydrogenase type 1
SRD5A2	steroid 5α-reductase type 2; 3-oxo-5α-steroid 4-dehydrogenase type 2
SRD5A3	steroid 5α-reductase type 3; 3-oxo-5α-steroid 4-dehydrogenase type 3

Conditions

Abbreviation	Full Name
21OHD	21-hydroxylase deficiency
BPH	benign prostatic hyperplasia
CAH	congenital adrenal hyperplasia
CP/CPPS	chronic prostatitis/chronic pelvic pain syndrome
CRPC	castration-resistant prostate cancer
DSD	disorder of sex development
PCOS	polycystic ovary syndrome

Other Abbreviations

Abbreviation	Full Name
ACTH	adrenocorticotropic hormone
HGNC	Human Genome Organisation Gene Nomenclature Committee
STAR	steroidogenic acute regulatory protein

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23. "Google Scholar search results for "5α-pregnan-17α-diol-3,11,20-trione" that is an incorrect name". 2022.
24. "Google Scholar search results for "5α-pregnane-17α-ol-3,20-dione" that is an incorrect name". 2022.
25. "IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN). The nomenclature of steroids. Recommendations 1989". *Eur J Biochem* **186** (3): 430. 1989. doi:10.1111/j.1432-1033.1989.tb15228.x. PMID 2606099. "3S-1.0. Definition of steroids and sterols Steroids are compounds possessing the skeleton of cyclopenta[a]phenanthrene or a skeleton derived therefrom by one or more bond scissions or ring expansions or contractions. Methyl groups are normally present at C-10 and C-13. An alkyl side chain may also be present at C-17.Sterols are steroids carrying a hydroxyl group at C-3 and most of the skeleton of cholestane."
26. "IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN). The nomenclature of steroids. Recommendations 1989". *Eur J Biochem* **186** (3). doi:10.1111/j.1432-1033.1989.tb15228.x. PMID 2606099. "3S-4. FUNCTIONAL GROUPS 3S-4.0. General Nearly all biologically important steroids are derivatives of the parent hydrocarbons (cf. Table 1) carrying various functional groups. [...] Suffixes are added to the name of the saturated or unsaturated parent system (see 33-2.5), the terminal e of -ane, -ene, -yne,

-adiene etc. being elided before a vowel (presence or absence of numerals has no effect on such elisions)."

27. *3S-1.4.* "IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN). The nomenclature of steroids. Recommendations 1989". *Eur J Biochem* **186** (3). 1989. doi:10.1111/j.1432-1033.1989.tb15228.x. PMID 2606099. "3S-1.4. Orientation of projection formulae When the rings of a steroid are denoted as projections onto the plane of the paper, the formula is normally to be oriented as in 2a. An atom or group attached to a ring depicted as in the orientation 2a is termed α (alpha) if it lies below the plane of the paper or β (beta) if it lies above the plane of the paper."
28. Favre, Henri; Powell, Warren (2014). "P-91". *Nomenclature of Organic Chemistry - IUPAC Recommendations and Preferred Names 2013.* The Royal Society of Chemistry. doi:10.1039/9781849733069. ISBN 978-0-85404-182-4. "P-91.2.1.1 Cahn-Ingold-Prelog (CIP) stereodescriptors Some stereodescriptors described in the Cahn-Ingold-Prelog (CIP) priority system, called 'CIP stereodescriptors', are recommended to specify the configuration of organic compounds, as described and exemplified in this Chapter and applied in Chapters P-1 through P-8, and in the nomenclature of natural products in Chapter P-10. The following stereodescriptors are used as preferred stereodescriptors (see P-92.1.2): (a) 'R' and 'S', to designate the absolute configuration of tetracoordinate (quadriligant) chirality centers;"
29. Favre, Henri; Powell, Warren (2014). "P-13.8.1.1". *Nomenclature of Organic Chemistry - IUPAC Recommendations and Preferred Names 2013.* The Royal Society of Chemistry. doi:10.1039/9781849733069. ISBN 978-0-85404-182-4. "P-13.8.1.1 The prefix 'de' (not 'des'), followed by the name of a group or atom (other than hydrogen), denotes removal (or loss) of that group and addition of the necessary hydrogen atoms, i.e., exchange of that group with hydrogen atoms.
As an exception, 'deoxy', when applied to hydroxy compounds, denotes the removal of an oxygen atom from an –OH group with the reconnection of the hydrogen atom. 'Deoxy' is extensively used as a subtractive prefix in carbohydrate nomenclature (see P-102.5.3)."
30. "IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN). The nomenclature of steroids. Recommendations 1989". *Eur J Biochem* **186** (3): 430. 1989. doi:10.1111/j.1432-1033.1989.tb15228.x. PMID 2606099. "3S-1.1. Numbering and ring letters Steroids are numbered and rings are lettered as in formula 1"
31. "IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN). The nomenclature of steroids. Recommendations 1989". *Eur J Biochem* **186** (3): 436–437. doi:10.1111/j.1432-1033.1989.tb15228.x. PMID 2606099. "3S-2.5 Unsaturation Unsaturation is indicated by changing -ane to -ene, -adiene, -yne etc., or -an- to -en-, -adien-, -yn- etc. Examples: Androst-5-ene, not 5-androstene 5α-Cholest-6-ene 5β-Cholesta-7,9(11)-diene 5α-Cholest-6-en-3β-ol Notes 1) It is now recommended that the locant of a double bond is always adjacent to the syllable designating the unsaturation. [...] 3) The use of Δ (Greek capital delta) character is not recommended to designate unsaturation in individual names. It may be used, however, in generic terms, like 'Δ^5-steroids'"
32. Favre, Henri; Powell, Warren (2014). "P-3". *Nomenclature of Organic Chemistry - IUPAC Recommendations and Preferred Names 2013.* The Royal Society of Chemistry. doi:10.1039/9781849733069. ISBN 978-0-85404-182-4. "P-31.2.2 General methodology 'Hydro' and 'dehydro' prefixes are associated with hydrogenation and dehydrogenation, respectively, of a double bond; thus, multiplying prefixes of even values, as 'di', 'tetra', etc. are used to indicate the saturation of double bond(s), for example 'dihydro', 'tetrahydro'; or creation of double (or triple) bonds, as 'didehydro', etc. In names, they are placed imme-

diately at the front of the name of the parent hydride and in front of any nondetachable prefixes. Indicated hydrogen atoms have priority over 'hydro' prefixes for low locants. If indicated hydrogen atoms are present in a name, the 'hydro' prefixes precede them."

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