The term "backdoor pathway" is sometimes used to specify different androgen steroidogenic pathways that avoid testosterone as an intermediate product. Although the term was initially defined as a metabolic route by which the 5α-reduction of 17α-hydroxyprogesterone ultimately leads to 5α-dihydrotestosterone, several other routes to 11-oxyandrogens have been discovered, which are also depicted as backdoor pathways. This review aims towards providing a clear, comprehensive definition that includes all currently known metabolic routes. Patient comprehension and the clinical diagnosis of relevant conditions such as hyperandrogenism can be impaired by the lack of clear and consistent knowledge on androgen backdoor pathways; the authors hope this review will accurately disseminate such knowledge to facilitate the beneficial treatment of such patients.

Introduction

The classic view of androgen steroidogenesis involves the combination of adrenal and gonadal pathways that ultimately convert cholesterol, via dehydroepiandrosterone (DHEA) and androstenedione (A4), to testosterone, which in turn converts to the potent androgen: 5α-dihydrotestosterone (DHT). In 2003, a metabolic route from 17α-hydroxyprogesterone (17-OHP), an intermediate in the canonical pathway, to DHT, that did not proceed through testosterone, was discovered in the tammar wallaby.[1] Shortly after this study, it was hypothesised that human steroidogenic enzymes are capable of catalyzing this backdoor pathwayand the potential clinical relevance in conditions involving androgen biosynthesis was proposed.[2] Since then, androgen steroidogenic backdoor pathways to potent 11-oxyandrogens have also been discovered and proposed as clinically relevant.[Barnard 2021] Thus there are a number of distinct androgen steroidogenic backdoor pathways which can confuse the search for clinical information. In addition to multiple pathways, various authors used different names for the same metabolic intermediates, further confusing matters. While naming inconsistencies are notoriously common when it comes to biomolecules,[3] establishing consensus names would facilitate accessibility to information. At the time of writing, the authors of the present review have submitted[4] these pathways to MetaCyc, a public database of metabolic pathways.[5]

This review intends to provide a unifying definition of the term "androgen backdoor pathway", a definition that encompasses recently discovered androgen steroidogenic pathways and jointly describes their relevance in the clinical context.

Androgen backdoor 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. An in depth understanding of androgen steroidogenesis can be crucial to the diagnosis of the patient.

History

In April 1987, Benjamin Eckstein and colleagues reported that 5α-androstane-3α,17β-diol (3α-diol), a direct precursor to DHT, is biosynthesized in immature rat testes in a

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pathway that predominantly involves 17-OHP but not androstenedione (A4) as an intermediate.[6]

In October 2000, Geoffrey Shaw and colleagues demonstrated that prostate formation in a marsupial (tammar wallaby pouch young) was mediated by the testicular androgen 3α-diol, which is higher in male than in female plasma during early sexual differentiation, identifying it as a key hormone in male development. They showed that 3α-diol acts in target tissues via DHT, i.e. is converted to DHT in target tissues, so that testosterone is not the only source of DHT.[7]

In February 2003, Jean Wilson and colleagues described that DHT, a 5α-reduced androgen, can be biosynthesized from both progesterone and 17-OHP by two pathways, with and without testosterone as an intermediate. They demonstrated that more 3α-diol is formed in the testes of tammar wallaby pouch young from progesterone than via testosterone. Thus the predominant pathway of 3α-diol formation is via 5α-pregnane-3α,17α-diol-20-one (5α-Pdiol) and androsterone (AST) as intermediates and not via androstenedione and testosterone as intermediates.[1]

In July 2004, Mala Mahendroo and colleagues described that 5α-androstane-3α,17β-diol (3α-diol) is the predominant androgen in immature mouse testes, and that it is formed by two pathways; the main one involves testosterone, and a second utilizes the pathway progesterone → 5α-dihydroprogesterone (5α-DHP) → 5α-pregnane-3α-ol-20-one (allopregnanolone, alloP5) → 5α-pregnane-3α,17α-diol-20-one (5α-Pdiol) → 5α-androstan-3α-ol-17-one (androsterone (AST)) → 5α-androstane-3α,17β-diol (3α-diol).[8]

In November 2004, Richard Auchus coined the term "backdoor pathway" in a review called "The backdoor pathway to dihydrotestosterone". He defined the backdoor pathway as a "route to DHT that does not involve the testosterone intermediate". He emphasized that this alternative pathway seems to explain how potent androgens are produced under certain normal and pathological conditions when the canonical androgen biosynthetic pathway cannot fully explain the observed consequences.[2]

It was in 2012 that Wudy and colleagues attributed, for the first time, the origin of androgen excess to the backdoor pathway in humans with 21-hydroxylase deficiency, which did not involve dehydroepiandrosterone (DHEA), A4, or testosterone as intermediates, but with higher urinary backdoor pathway metabolites.[14]

In July 2013, Amanda Swart and colleagues demonstrated that C11-oxyandrogens produced in the adrenal gland may contribute to the androgenic activity in humans with 11-ketotestosterone (11-KT) activity similar to that of testosterone, and 11-ketodihydrotestosterone (11-KDHT) similar to that of DHT, while the activity of 11β-hydroxytestosterone (11-OHT) and 5α-dihydro-11β-hydroxytestosterone (11-OHDHT) is about half of that of testosterone and DHT, respectively. The authors demonstrated that the pathways towards those 11-keto and 11β-hydroxy androgens bypass testosterone intermediary.[9][Bloem 2015] Her group has subsequently also described

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the C11-oxy progesterone backdoor pathway further contributing to active androgens. [41][42][46]

Definition

The central feature that distinguishes the canonical[10][11][12] androgen steroidogenesis pathway from backdoor pathways is the involvement of testosterone (Figure 1). In the canonical pathway, 5α-dihydrotestosterone (DHT) is biosynthesized directly from testosterone by 5α-reduction. Therefore, this paper proposes that any androgenic steroidogenic pathway that does not involve testosterone but produces potent androgens is an androgen backdoor pathway. This definition subsumes both the generation of DHT from 17α-hydroxyprogesterone (17-OHP) with roundabout of testosterone, and the generation of 11-oxy androgen products from the C11-oxyandrogen (C11-oxy C_{19}) and C11-oxyprogesterone (C11-oxy C_{21}) metabolic pathways that are not derived from testosterone and have a potency comparable to that of DHT.

Although some metabolic intermediates can be technically considered as androgens, not all androgens are necessarily potent or clinically relevant agonists of the androgen receptors.

The routes to 5α-dihydrotestosterone

In canonical androgen steroidogenesis, a 5α-reductase enzyme catalyzes the direct chemical reaction from testosterone to 5α-dihydrotestosterone (DHT). However, in a backdoor pathway, this enzyme first 5α-reduces one of the following steroids: 17α-hydroxyprogesterone (17-OHP), progesterone, or androstenedione (A4), which are ultimately converted to DHT. The enzymes that take part in both canonical and backdoor pathways are the same, it is the order of reaction that makes the difference. While in a backdoor pathway 5α-reduction of a steroid is the first step, in the canonical pathway it is the last.

5α-reduction of 17α-hydroxyprogesterone

The first metabolic route that falls under the definition of an androgen backdoor pathway can be described as 5α-reduction of 17α-hydroxyprogesterone (17-OHP) that is finally converted to 5α-dihydrotestosterone (DHT) within a set of enzymatic transformations that bypass the conventional intermediates A4 and testosterone.

In mammals, backdoor route is activated during normal prenatal development and leads to early male sexual differentiation.[11][13][7][8] The route was first described in the marsupials and later confirmed in humans.[15] This route is essential for the development of the penis.[11] Both the classical and backdoor pathways of androgen biosynthesis are required for normal human male genital development.[13]

In congenital adrenal hyperplasia (CAH) due to cytochrome P450c21 (21-hydroxylase) deficiency[14] including late-onset non-classical forms,[16] or cytochrome P450

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oxidoreductase deficiency,[17] this route may be activated regardless of age and sex by even a mild increase in circulating 17-OHP levels.[18][16] Cytochrome P450c21 (CYP21A2) is encoded by *CYP21A2* gene in humans.[Higashi et al 1986]

In the production of androgens, the Δ^5 reaction (from pregnenolone to 17α-hydroxypregnenolone to DHEA) and the Δ^4 reaction (from progesterone to 17-OHP to A4) are catalysed by cytochrome P450c17 (17α-hydroxylase/17,20-lyase, CYP17A1) in the adrenal and gonads. However, the catalytic efficiency of the 17,20-lyase for 17-OHP is about 100 times lower than the 17,20-lyase for 17α-hydroxypregnenolone, resulting in negligible A4 being produced in the Δ^4 reaction pathway in humans. The accumulation of 17-OHP in 21-hydroxylase deficiency can be attributed 17-OHP which is a primary substrate for CYP21A2, expressed in the adrenal and not the gonads. [Miller 2005][Miller 2019]

This metabolic route consists of five steps:

1. The first step of this route is the conversion of 17-OHP by 5α-reductase isozymes, the 3-oxo-5α-steroid 4-dehydrogenase type 1 (5αRed1, SRD5A1) and type 2 (5αRed2, SRD5A2), encoded in humans by *SRD5A1* and *SRD5A2* genes, respectively.[Normington & Russell 1992] The conversion is done by 5α-reduction of 17-OHP to 5α-pregnan-17α-ol-3,20-dione (Figure 2), also known as 17α-hydroxy-dihydroprogesterone (5α-Pdione or 17-OH-DHP).[14][Gupta et al 2003] [41]

2. 17-OH-DHP is then converted to 5α-pregnane-3α,17α-diol-20-one (5α-pdiol) via 3α-reduction by a 3α-hydroxysteroid dehydrogenase isozyme (AKR1C2/AKR1C4[11][15] or 17β-hydroxysteroid dehydrogenase type 6 (17βHSD6), encoded by the *HSD17B6* gene in humans, that also has the 3α-reduction activity was shown by Muthusamy et al.[Muthusamy et al 2011]

3. 5α-pdiol is then converted to 5α-androstan-3α-ol-17-one (androsterone (AST)) by 17,20-lyase activity of cytochrome P450c17 (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).[14][11]

4. Androsterone, in its turn, is 17β-reduced to 5α-androstane-3α,17β-diol (3α-diol) by 17β-hydroxysteroid dehydrogenase type 3 or type 5. Type 3 (17βHSD3) is encoded by the *HSD17B3* gene in humans. The type 5 (17βHSD5), sometimes also abbreviated as HSD17B5, is actually an aldo-keto reductase family 1 member C3, encoded by the AKR1C3 gene in humans.[12]

5. The final step is 3α-oxidation of 3α-diol in target tissues to DHT by several 3α-oxidoreductases (RL-HSD (HSD17B6), HSD17B10, RODH4, RDH5, and DHRS9).[17] It is a reverse oxidative step not required in the canonical pathway.

Therefore, the pathway can be outlined as 17α-hydroxyprogesterone (17-OHP) → 5α-pregnan-17α-ol-3,20-dione (17-OH-DHP) → 5α-pregnane-3α,17α-diol-20-one (5α-pdiol) → 5α-androstan-3α-ol-17-one (androsterone) → 5α-androstane-3α,17β-diol (3α-diol) → 5α-dihydrotestosterone (DHT).[23] [14] [19][13]

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5α-reduction of progesterone [edit | edit source]

This pathway is similar to the one described above, but the initial substrate for 5α-reductase is progesterone rather than 17-OHP. This route is also activated in mammals during normal male prenatal development, and have been confirmed first in mice[8] and later in humans[11].This route may also be a consequence of abnormally upregulated 5αRed1, such as in polycystic ovary syndrome (PCOS)[24][25][26][Marti et al] or in prostate cancer[12].

In male fetuses, placental progesterone acts as a substrate during the synthesis of backdoor androgens, which occur in multiple tissues. Enzymes related to the backdoor pathway of male fetuses are mainly expressed in non-gonadal tissues, and the steroids involved in this pathway are also primarily present in non-gonadal tissues.[11] If this pathway is disrupted, it will lead to disordered sex development, i.e., the failure of normal masculinization.[15][19]

The first step in this pathway is 5α-reduction of progesterone towards 5α-dihydroprogesterone (5α-DHP) by 5αRed1. 5α-DHP is then converted to 5α-pregnane-3α-ol-20-one (allopregnanolone) via 3α-reduction by a 3α-hydroxysteroid dehydrogenase isozyme (AKR1C2/AKR1C4). Allopregnanolone is then converted to 5α-pdiol by the 17α-hydroxylase activity of cytochrome P450c17. Then this metabolic route proceeds to DHT the same way as the pathway that started with 17-OHP.[11]

Therefore, the pathway can be outlined as: progesterone → 5α-dihydroprogesterone (5α-DHP) → 5α-pregnane-3α-ol-20-one (allopregnanolone) → 5α-pregnane-3α,17α-diol-20-one (5α-pdiol) → 5α-androstan-3α-ol-17-one (androsterone, AST) → 5α-androstane-3α,17β-diol (3α-diol).

5α-reduction of androstenedione [edit | edit source]

The production of DHT proceeds along 2 pathways (i) conversion of A4 to testosterone and then to DHT or (ii) the 5a-reduction of A4 followed by the conversion of the intermediate to DHT. In prostate cancer, 5αRed1 is highly expessed and reduces androstenedione (A4) to 5α-androstane-3,17-dione (5α-dione), which can be converted directly to DHT by 17βHSD3 / 17βHSD5. So, the backdoor pathways that starts from A4 can be outlined as following:[27]

Pathway (i) “normal” production of DHT

androstenedione (A4) → 5α-androstane-3,17-dione (5α-dione) → AST
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testosterone → 5α-dihydrotestosterone(DHT) → 3α-diol

Pathway (ii) alternative pathway

androstenedione (A4) → 5α-androstane-3,17-dione (5α-dione) → dihydrotestosterone (DHT).

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The routes to11-oxyandrogens [edit|editsource]

The other routes that fall under the definition of the androgen backdoor pathway, lead to production of 11-oxyandrogens. These 19-carbon steroids contain either an hydroxyl group or a keto (also termed oxo) group covalently bound to the carbon atom at position 11, also erroneously termed 11-oxygenated androgens: 11-ketotestosterone (11-KT) and 11-ketodihydrotestosterone (11-KDHT), which are 11-keto forms of testosterone and DHT, respectively, and having similar potency,[9] and while 11OHA4 and 11-ketoandrostenedione (11KA4) are not regarded as active androgens, at higher concentrations these steroids are able to activate the androgen receptor,.[Bloem et at 2015] which may be relevant in steroidogenic tissue, particularly in clinical conditions associated with androgen excess.

The biosynthesis of 11-oxyandrogens in this pathway does not require testosterone or DHT as intermediate products. 11-oxyandrogens are potent and clinically relevant agonists of the androgen receptors.[9] [Bloem et al 2015] 11-KT may serve as the main androgen for healthy women.[Nanba et al 2019] 11-oxy androgens may be produced in physiological quantities in healthy mammalian organisms,[Rege et al 2019] and in excessive quantities in the pathological conditions like CAH due to 21-hydroxylase deficiency,[31][32] PCOS,[33][Kempegowda et al 2020] benign prostatic hyperplasia (BPH),[34] in prostate cancer,[9][12][35]][du Toit & Swart 2018][du Toit et al 2017] testicular adrenal rest tumors[30][36][38] and disorders of sex development in neonates and in children.[37][17][du Toit & Swart 2021]

~~There are several routes that may lead to the production of 11-oxyandrogens, particularly, to 11-KT and 11-KDHT, however, cytochrome P450 11β-hydroxylase (CYP11B1) enzyme remains the initial step of the pathway towards 11-oxyandrogen production.[34] Humans have two isozymes with 11β-hydroxylase activity, encoded by the genes CYP11B1 (regulated by ACTH) and CYP11B2 (regulated by angeotensin, II).[39] The initial step is one of the following:~~

~~17-OHP is converted to 21-deoxycortisol.[40][41] Progesterone is converted to 11β-hydroxyprogesterone.[42] There are multiple studies conducted since 1987 that demonstrate increased levels of 11β-hydroxyprogesterone in congenital adrenal hyperplasia due to 21-hydroxylase deficiency.[43][44][45] *In vitro* studies predict that excess of 11β-hydroxyprogesterone may ultimately leads to production of 11-KDHT and 11-ketoandrosterone.[46][42][34] The *in vitro* catalytic activity (min^{-1}) of 11βOH for progesterone is 12.3, comparing to 96.8 for 11-deoxycortisol, the main substrate of CYP11B1.[47] This probably explains the reasons why, in situation of 21-hydroxylase deficiency, when the 11βOH enzyme has not enough 11-deoxycortisol, its main substrate, this enzyme begins to catalyze 11β-hydroxylation of another steroid avialable - progesterone. In a 2015 study, Turcu and colleagues demonstrated that in CAH patients levels of 11-deoxycortisol were five~~

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~~times lower than in healthy controls, but the levels of progesterone were twice higher.[38]~~

~~A4 is converted to 11β-hydroxyandrostenedione (11-OHA4).[34][16] Because 11βOH in humans is predominantly expressed in adrenals, 11-OHA4 can be used as a biomarker of adrenal origin of androgen excess in women – if the primary source of androgen excess is adrenal, then levels of 11-OHA4 are higher then those of A4, but if the source is ovarian, the levels of 11-OHA4 are lower then those of A4. Therefore, the ratio of A4 to 11-OHA4 is an important marker of adrenal androgen excess in women known since 1980 in CAH,[48] PCOS[49] and hirsutism.[50]~~

~~The exact order of steps in metabolic routes towards 11-oxygenated androgens in humans is not yet fully elucidated, however, the order in which enzymes catalyze reactions in the pathway towards 11-KDHT is presumably mostly the same as in the backdoor pathway from 17-OHP to DHT.[42] The key enzyme, however, for the production of 11-oxygenated androgens, is 11βOH - an enzyme expressed mainly in adrenals.[42][35][51] Therefore, 11-oxygenated androgens are considered androgens of adrenal origin. They follow the circadian rhythm of cortisol but correlate very weakly with testosterone, which further supports their adrenal origin and ACTH governance.[52] However, in addition to the adrenal glands, 11βOH is also expressed in Leydig cells and ovarian theca cells, albeit at lower levels, so the production of 11-KT precursors may be one of the most important functions of 11βOH in the gonads.[53]~~

There are several routes that may lead to the production of 11-oxyandrogens, particularly, to 11-KT and 11-KDHT, however, cytochrome P450 11β-hydroxylase (CYP11B1) enzyme remains the initial step of the pathway towards 11-oxyandrogen production.[35] [Haru et al][Schloms et al 2012] Humans have two isozymes with 11β-hydroxylase activity, encoded by the genes *CYP11B1* (regulated by ACTH) and *CYP11B2* (regulated by angiotensin, II).[39] In the adrenal the two isozymes catalyse the production of both C11-oxyandrogens, 11OHA4[Haru et al][Schlomset al][35] and 11β-hydroxytestosterone (11-OHT) from testosterone[35] as well as the production of C11-oxyprogesterones: 4-pregnen-11β-ol-3,20-dione (also known as 21-deoxycorticosterone and 11β-hydroxyprogesterone (11OHP))[42] and 4-pregnen-11β,17α-diol-3,20-dione (also known as 11β,17α-dihydroxyprogesterone, 21-deoxycortisol (21dF)).[41]

Since CYP11B isozymes are predominantly expressed in adrenals 11-oxyandrogens are considered androgens of adrenal origin. They follow the circadian rhythm of cortisol but correlate very weakly with testosterone, which further supports their adrenal origin and ACTH governance.[52] However, in addition to the adrenal glands, CYP11B1 is also expressed in Leydig cells and ovarian theca cells, albeit at far lower levels, so the production of 11-KT precursors may be one of the most important functions of 11β-hydroxylase activity in the gonads.[53] It had been suggested that 11β-hydroxyandrostenedione (11-OHA4) and its urinary metabolites could have

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clinical applications used as a biomarkers of adrenal origin of androgen excess in women. Increased adrenal 11OHA4 production was characterised, using changes in A4:11OHA4 and 11β-hydroxyandrosterone:11β-hydroxyetiocholanolone ratios, in cushing syndrome, hirsutism, CAH and PCOS,[48][Lipsett & Ritter][Barnard et al 2021] [49] However, due to to conflicting reports ratios did not find a firm footing in the clinical as a diagnostic tool.

Another prerequisite enzyme in the production of C11-oxyandrogens, is 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2, HSD11B2) which converts 11OHA4 to 11ketoandrostenedione and 11OHT to 11KT[35][Gent et al 2019b][Gent et al 2019a]. The production of 11KA4 and 11KT takes place in the periphery and the a lesser extent in the adrenal. These four C11-oxyandrogens are further converted by 5α-reductase which catalyses the production of 11-5α-dione and 11KDHT following a pathway similar to that of the canonical androgen steroidogenesis pathway.[35][9][Swart& Storbeck 2015]

This metabolic route consists of a number of steps:

1. The C11-oxyandrogens, 11OHA4 and 11β-hydroxytestosterone (11OHT), are produced by the CYP11B isozymes from A4 and testosterone, respectively.

2. 11OHA4 and 11OHT are then converted by 11βHSD2 in the production of their C11-keto forms, 4-androsten-3,11,17-trione (11KA4) and 4-androsten-17β-ol-3,11-dione (11KT), respectively. These four C11-oxyandrogens, 11OHA4, 11OHT 11KA4, and 11KT are ultimately converted to 11KDHT following the same metabolic route of A4 and T.

3. The next step of this route is the conversion of 11OHA4, 11KA4, 11OHT and 11KT by 5α-reductase isozymes, SRD5A1 and SRD5A2 to 5α-androstan-11β-ol-3,17-dione (11OH5α-dione), 5α-androstane-3,11,17-trione (11K-5αdione), 5α-androstan-11β,17β-diol-3-one (also known as 11β-hydroxydihydrotestosterone (11OHDHT)) and 5α-androstan-17β-ol-3,11-dione also known as 11keto-dihydrotestosterone 11KDHT, respectively.

4. 11OH5α-dione, 11K5α-dione, 11OHDHT and 11KDHTare then converted to the inactive forms of these C11-oxyandrogens, 5α-androstan-3α,11β-diol-17-one (also. Known as 11-hydroxyandrosterone (11OHAST)), 5α-androstan-3α-ol-11,17-dione (also known as 11keto-androsterone (11KAST)), 5α-androstan-3α,11β,17β-triol (11OH-3αdiol) and 5α-androstane-3α,17β-diol-11-one (11K-3αdiol) via 3α-reduction by a 3α-hydroxysteroid dehydrogenase isozyme. However, this reaction is reversible and so these inactive androgens can be reactivated putting 11KDHT and 11OHT back into the system

5. These C11-oxyandrogens are also converted by17βHSD3, 17βHSD5 (AKR1C3) and by 17βHSD2. 11KA4, 11K5α-dione and 11KAST can be converted to 11KT, 11KDHT and 11K-3αdiol by 17βHSD3 and 17βHSD5, respectively. 11OHA4, 11OHAST and 11OH5α-dione are not converted to 11OHT, 11OHDHT or 11OH-3adiol as these C11-hydroxyandrogens and not substrates for 17βHSD3 or 17βHSD5.

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However, 17βHSD2 converts 11OHT and 11OHDHT to 11OHA4 and 11OH5α-dione, respectively. 17βHSD2 also converts 11KT, 11KDHT and 11K-3αdiol back to 11KA4, 11K5α-dione and 11KAST.

6. Further adding to the complexity of these reactions is the fact that 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1) can convert all of the C11-keto androgens back to the C11-hydroxy androgens.

These complex pathways leading to the production of 11KT, 11KDHT and 11OHDHT from 11OHA4 and 11OHT set out above have been fully characterised by Swart and colleagues and can be simplistically outlined as follows:

A4 → 11OHA4 → 11KA4. → 11KT
↓ ↓ ↓
11OH-5α-dione. → 11K-5α-dione → 11KDHT → 11OHDHT
↓ ↓ ↓ ↓
11OHAST 11KAST 11K-3αdiol → 11OH-3αdiol.

Or

A4 → 11OHA4 ⇄ 11KA4. ⇄ 11KT
↓ ↓ ↓
11OH-5α-dione. ⇄ 11K-5α-dione ⇄ 11KDHT ⇄ 11OHDHT
⇅ ⇅ ⇅ ⇅
11OHAST 11KAST 11K-3αdiol → 11OH-3αdiol.

And

T →11OHT → 11KT
↓ ↓
11OH-3αdiol → 11OHDHT → 11KDHT →11K-3αdiol

or

T →11OHT ⇄ 11KT
↓ ↓
11OH-3αdiol ⇄ 11OHDHT → 11KDHT ⇄11K-3αdiol

The initial step in the production of C11-oxyandrogens from the progesterones is that of 17-OHP converted to 21-deoxycortisol[41] and that of progesterone to 11β-hydroxyprogesterone.[42] Multiple studies have been conducted by Fiet and colleagues since 1987 that demonstrate increased levels of 11β-hydroxyprogesterone in congenital adrenal hyperplasia due to 21-hydroxylase deficiency.[43][44][45] *In vitro* studies predict that excess of 11β-hydroxyprogesterone may ultimately leads to

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production of 11-KDHT and 11-ketoandrosterone.[46][42] Investigating the *in vitro* catalytic activity (min^{-1}) of CYP11B1 and CYP11B2 both enzymes have been shown to convert progesterone, androstenedione and testosterone, indicated the importance of the keto group of the A-ring in the steroid nucleus and the potential of androgens and progesterones serving as substrates for the CYP11B isozymes.[47] The biosynthesis of 11OHP4 and 21-deoxycortisol may be attributed to 21-hydroxylase deficiency resulting in increased progesterone and 17OHP4 concentrations and, together with the unavailability of CYP11B's main substrates, deoxycortisol and deoxycorticosterone, drive the production of C11-oxy progesterones

The C11-oxyprogesterones, 11OHP4 and 21dF, catalysed by the CYP11B isozymes also require 11βHSD2 in the production of the C11-keto forms: 4-pregnen-3,11,20-trione (also known as 11keto-progesterone (11KP4) and 4-pregnen-17α-ol-3,11,20-trione (also known as 21-deoxycortisone (21dE), respectively [41][42][46]Gent et al 2019b][Gent et al 2019a]. These four C11-oxyprogesterones, 11OHP4, 21dF, 11KP4 and 21dE are ultimately converted to 11KDHT following the same metabolic route of 17-OHP4, consisting of five steps

1. The first step of this route is the conversion of 11OHP4, 11KP4, 21dF and 21dE by 5α-reductase isozymes, SRD5A1 and SRD5A2 to 5α-pregnane-11β-ol-3,20-dione (11OH-DHP4), 5α-pregnane-3,11,20-trione (11KDHP4), 5α-pregnan-11β,17α-diol-3,20-dione (11OH-Pdione) and 5α-pregnane-17α-diol-3,11,20-trione (11KPdione)

2. 11OH-DHP4, 11KDHP4, 11OH-Pdione and 11KPdione are then converted to 5α-pregnane-3α,11β-diol-20-one (3,11diOH-DHP4), 5α-pregnane-3α-ol-11,20-dione (alfaxalone), 5α-pregnane-3α,11β,17α-triol-20-one (11OHPdiol) and 5α-pregnane-3α,17α-diol-11,20-dione (11KPdiol) via 3α-reduction by a 3α-hydroxysteroid dehydrogenase isozyme.

3. 11diOH-DHP4, alfaxalone, 11OHPdiol and 11KPdiol are then converted to 5α-androstane-3α,11β-diol-17-one (11OHAST) and 5α-androstane-3α-ol-11,17-dione (11KAST) by CYP17A1. In these reactions 11OHPdiol and 11KPdiol are converted to C_{19} steroids by the 17,20-lyase activity of cytochrome P450c17 (CYP17A1) which cleaves a side-chain (C17-C20 bond) from the steroid nucleus, converting a C_{21} steroid (a pregnane) to a C_{19} steroid (androgen). In the conversion of 11diOH-DHP4 and alfaxalone to androgens these steroids first undergo the hydroxylase activity and then the 17,20-lyase activity of cytochrome P450c17. [van Rooyen et al 2020]

4 11OHAST is first converted to 11KAST by 11βHSD2 since is not a substrate for 17βHSD. the next enzyme in the pathway,17βHSD3 or 17βHSD5.

11KAST is now either converted to 11K3α-diol by 17β-hydroxysteroid dehydrogenase type 3 or type 5. Type 3 (17βHSD3) or type 5 (17βHSD5, AKR1C3,) or it may be converted to 11KAdione by the 3α-oxidation activity of 17βHSD6, depending on enzyme expression levels and steroidogenic tissue.

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5 11KDHT is subsequently biosynthesised from both 5α-androstane-3α,17β-diol-11-one (11K3α-diol) and 5α-androstane-3,11,17-trione (11K-5αdione). 11K3α-diol is converted by 17βHSD6 and 11K-5αdione is converted by 17βHSD3 and 17βHSD5. In addition, 11KDHT can be converted to 11OHDHT by 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1, HSD11B1).

These pathways leading to the production of 11KT, 11KDHT and 11OHDHT from progesterone and 21-dF have been fully characterised by Swart and can be outlined as follows:

P4 → 11OHP4 → 11KP4
↓ ↓
11OH-DHP4 → 11K-DHP4
↓ ↓
3,11diOH-DHP4 → alfaxalone
↓ ↓
11OHAST → 11KAST
↓ ↓
11K-3αdiol → 11KDHT → 11OHDHT

Or

P4 → 11OHP4 ⇄ 11KP4
↓ ↓
11OH-DHP4 ⇄ 11K-DHP4
↑↓ ↑↓
3,11diOH-DHP4 ⇄ alfaxalone
↑↓ ↑↓
11OHAST ⇄ 11KAST
↑↓ ↑↓
11K-3αdiol ⇄ 11KDHT ⇄ 11OHDHT

And

17OHP4 → 21dF → 21dE
↓ ↓
11OHPdione → 11KPdione
↓ ↓
11OHPdiol → 11KPdiol
↓ ↓
11OHAST → 11KAST → 11K-5αdione
↓ ↓
11K-3αdiol → 11KDHT → 11OHDHT

Or

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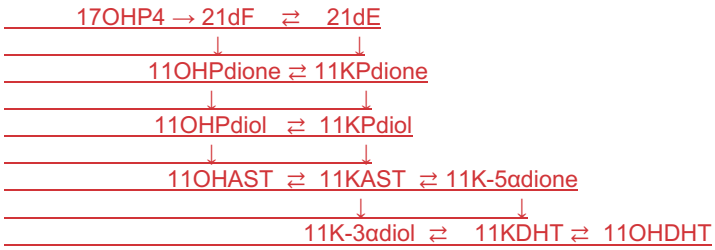

The order of steps in metabolic routes of the C11-oxyprogesterones towards 11-oxygenated androgens have been fully characterised by Swart, with the order in which same enzymes catalyze reactions in the pathway towards 11-KDHT and 11OHDHT similar, in part, to 17-OHP's conversion to DHT in the backdoor pathway.[41][van Rooyen 2022][42] However, in the biosynthesis of 11-oxy androgens and 11-oxy prgesterones, additional key enzymes for the initial reactions, are cytochrome P450 11β-hydroxylase and 11β- hydroxysteroid dehydrogenase [42][35][Gent et al 2019b][Gent et al 2019a]_ with CYP11B expressed primarily in adrenals together with low levels of 11βHSD[Rege et al 2013] which is more abundantly expressed in peripheral tissue. Once converted by 5α-reductase, the pathway followed is similar to that of the backdoor steroidogenesis pathway leading ultimately to 11KDHT.

ClinicalSignificance [edit|editsource]

Androgen backdoor pathways are not always considered in the clinical evaluation of patients with hyperandrogenism, i.e., androgen excess. Hyperandrogenism may lead to symptoms like acne, hirsutism, alopecia, premature adrenarche, oligomenorrhea or amenorrhea, polycystic ovaries and infertility.[54][55] Despite the prevailing dogma that testosterone and DHT are the primary human androgens, this paradigm applies only to healthy men.[51] Although testosterone has been traditionally used as a biomarker of androgen excess[56] it correlates poorly with clinical findings of androgen excess.[51] If testosterone levels appear to be normal, ignoring the backdoor pathway may lead to diagnostic flaws and confusion, since hyperandrogenism may be caused by very potent androgens, such as DHT and the 11-oxyandrogens, 11KT and 11KDHT produced by a backdoor pathway.[57] [58] Another issue with the use of testosterone as a biomarker of androgen excess is the low circulating levels in women and the specificity and sensitivity of the assays used.[56][Nanba et al 2019][33] In a 2017 study, O'Reilly and colleagues revealed that 11-oxyandrogens are the predominant androgens in women with PCOS, while in healthy control subjects, classic androgens constitute the majority of the circulating androgen pool; nevertheless, the levels of 11-KT exceeded those of testosterone in both groups, specifically, 3.4 fold in the PCOS group. Besides that, the levels of 11-OHA4 and 11-ketoandrostenedione correlated with the levels of markers of insulin resistance; therefore, the study suggests that androgen excess precedes androgen-driven insulin resistance in PCOS.[33] While

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earlier studies had commonly only measured 11OHA4 or 11-ketoandrosterone (11OHAST) and 11β-hydroxyetiocholanolone (11OHEt), urinary metabolites of 11OHA, [Barnard et al 2021] more recent investigations have reorted circulating levels of 11KA4, 11KT and 11OHT levels in PCOS as well as C11-oxyprogesterones. In another 2016 study, Turcu and colleagues showed that in classic CAH due to 21-hydroxylase deficiency, in male and female patients which received glucocorticoid therapy, both conventional and 11-oxygenated androgens were elevated 3-4 fold compared to healthy controls. The exceptions were DHEA, dehydroepiandrosterone sulfate (DHEA-S), and androstenediol sulfate (A5-S), whose levels were 6.0, 7.5, and 9.4 times lower, respectively, in the patients with the condition compared to healthy controls, due to suppression by glucocorticoid treatment of the patients. The levels of 11-oxygenated androgens correlated positively with conventional androgens in women but negatively in men. The levels of 11-KT were 4 times higher compared to that of testosterone in women with the condition. [31] A subsequent study reported 11OHT was the only significantly elevated C11-oxy androgen in PCOS and together with11KT, correlated with BMI. [Yoshidaet al 2018] Significantly elevated 11KT levels have been detected in the daughters of PCOS mothers and in obese girls while 11OHA4, 11KA4 and 11OHT levels were comparable. [Torchen al 2020] 11KT has also been shown to be elevated together with decreased 11KA4 levels in PCOS patients with micronodular adrenocortical hyperplasia. In addition 11OHAST, 11OHEt, DHP4 and 11K-DHP4 levels were elevated and 11OHP4, 21dF and 11KDHP4 were elevated in in patients with inadequate dexamethasone responses.[26]

In a 2018 study, Rege and colleagues demonstrated that levels of 11-KT in girls aged between 4 and 7 years during normal adrenarche (healthy controls) exceeded those of testosterone by 2.43 times, and in those with premature adrenarche by 3.48 times. However, the levels of testosterone in girls with premature adrenarche were higher by just 13% compared to age-matched healthy controls.[59]

Unlike testosterone and A4, androgens produced by the backdoor pathway, i.e., DHT, 11-KT and other 11-oxyandrogens, are not converted by aromatase into estrogens in vivo.[60][61] The inability of aromatase to convert the 11-oxyandrogens to estrogens may contribute to the C11-oxyandrogens circulating at higher levels than other androgens when not taking into account dehydroepiandrosterone (DHEA).

In some cases of advanced prostate cancer, androgen deprivation therapy related to gonadal testosterone depletion does not produce long-term effects, and metastatic tumors may develope into castration-resistant prostate cancer (CRPC). The development of CRPC depends on adrenal precursor steroids to produce dihydrotestosterone in the tumor in metabolic pathways in which testosterone is not involved. Instead, 5αRed1, expression of which increases in CRPC, 5α-reduces A4 to 5α-androstane-3,17-dione (5α-dione), which is then converted to DHT.[27][12] Therefore, DHT produced within a backdoor pathway hampers the androgen

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deprivation therapy. Although blood testosterone levels are reduced by 90-95% in men whose testicles have been removed, DHT in the prostate is only reduced by 50%, thus indicating the presence of a metabolic pathway in the prostate that does not require testicular testosterone to produce DHT.[62] In a 2021 study, Snaterse and colleagues demonstrated that 11-KT is the most circulating active androgen in 97% of CRPC patients, accounting for 60% of the total active androgen pool.[63] Besides that, in CPRC, 11-oxyandrogens contribute significantly to the androgen pool.[12] The full range of androgen pathway metabolites have been shown in normal prostate and various prostate cancer cell models. 11OHA4 and 11OHT are both converted to potent androgens, 11KT and 11KDHT. Compared to testosterone and DHT, C11-oxy androgens were most the predominant androgens. High levels of 11KT, 11KDHT and 11OHDHT have also been detected in prostate cancer tissue (~10–20 ng/g) and in circulation, 11KT (~200–350nM) and 11KDHT (~20nM) being the most abundant. Furthermore, glucuronidation of the C11-oxyandrogens is hampered by the C11-oxy group in prostate cancer cell models while in PCa patients' plasma 11KDHT was present only in the unconjugated form, with 11KT also predominantly unconjugated. [du Toit et al 2017] [du Toit et al 2018] The contribution of the C11-oxyandrogens as well as the C11-oxyprogesterones to active androgens have also been demonstrated in BPH cell models showing the conversion of 11OHP4 and 11KP4 in the backdoor pathway resulting in the production of 11KDHT. Backdoor pathway intermediates were also detected in BPH tissue as well as in circulation in BPH patients. [34] Androgens play a vital role in the development, growth and maintenance of the prostate. Therefore, the role of androgens should be seriously considered not only in prostate cancer, but also in clinical conditions such as BPH[62] and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).[64] In a 2008 study, Dimitrakov and colleagues demonstrated that in men with CP/CPPS, there were more cases of such steroid abnormalities compared to healthy controls that suggested CYP21A2 deficiency in patients with CP/CPPS.[64] Such deficiency is usually associated with elevated androgens produced by backdoor pathways. Therefore, assessing the activity of CYP21A2 and the C11-oxyandrogens and C11-oxyprogesterones in these patients may elucidate the

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causes of CP/CPPS and indicate that CP/CPPS may be consequence of a systemic condition of androgen excess but not a disease that originates in the prostate.

PubChemCIDs [edit|editsource]

In order to unambiguously define all the steroids mentioned in the present review, their respective PubChem IDs are listed below. PubChem is a database of molecules, maintained by the National Center for Biotechnology Information of the United States National Institutes of Health. The IDs given below are intended to eliminate ambiguity caused by the use of different synonyms for the same metabolic intermediate by different authors when describing the androgen backdoor pathways.

11-deoxycortisol: 440707; 11-KDHT: 11197479; 11-ketoandrostenedione: 223997; 11-ketoandrosterone: 102029; 11-KT: 104796; 11β-hydroxyandrostenedione: 94141; 11β-hydroxyprogesterone: 101788; 17-OHP: 6238; 17-OH-DHP: 11889565; 21-deoxycortisol: 92827; 3α-diol: 15818; 5α-DHP: 92810; 5α-dihydroprogesterone: 92810; 5α-dione: 222865; 5α-pdiol: 111243; A4: 6128; A5: 10634; A5-S: 13847309; allopregnanolone: 92786; androsterone: 5879; DHEA: 5881; DHEA-S: 12594; DHT: 10635.

Abbreviations [edit|editsource]

11βOH 11β-hydroxylase
17-OH-DHP 5α-pregnan-17α-ol-3,20-dione
17-OHP 17α-hydroxyprogesterone
3α-diol 5α-androstane-3α,17β-diol
17βHSD3 17β-hydroxysteroid dehydrogenase type 3, HSD17B3
17βHSD5 17β-hydroxysteroid dehydrogenase type 5, HSD17B5, also the aldo-keto reductase family 1 member C3, AKR1C3 **17βHSD6** 17β-hydroxysteroid dehydrogenase type 6, HSD17B6
5α-DHP 5α-dihydroprogesterone
5α-dione 5α-androstane-3,17-dione
5α-pdiol 5α-pregnane-3α,17α-diol-20-one
5αRed1 3-oxo-5α-steroid 4-dehydrogenase type 1, SRD5A1
5αRed2 3-oxo-5α-steroid 4-dehydrogenase type 2, SRD5A2
A4 androstenedione
A5 androstenediol
A5-S androstenediol sulfate
Allopregnanolone 5α-pregnane-3α-ol-20-one
Androsterone 5α-androstan-3α-ol-17-one
BPH benign prostatic hyperplasia
CAH congenital adrenal hyperplasia
CP/CPPS chronic prostatitis/chronic pelvic pain syndrome
CRPC castration-resistant prostate cancer
DHEA dehydroepiandrosterone
DHEA-S dehydroepiandrosterone sulfate
DHT 5α-dihydrotestosterone
PCOS polycystic ovary syndrome

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