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The role of 5-reduction in physiology and metabolic disease: evidence from cellular, pre-clinical and human studies

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ABSTRACT

The 5-reductases (5α-reductase types 1, 2 and 3 [5αR1−3], 5β-reductase [5βR]) are steroid hormone metabolising enzymes that hold fundamental roles in human physiology and pathology. They possess broad substrate specificity converting many steroid hormones to their 5α- and 5β-reduced metabolites, as well as catalysing crucial steps in bile acid synthesis. 5αRs are fundamentally important in urogenital development by converting testosterone to the more potent androgen 5α-dihydrotestosterone (5αDHT); inactivating mutations in 5αR2 lead to disorders of sexual development. Due to the ability of the 5αRs to generate 5αDHT, they are an established drug target, and 5αR inhibitors are widely used for the treatment of androgen-dependent benign or malignant prostatic diseases.

There is an emerging body of evidence to suggest that the 5-reductases can impact upon aspects of health and disease (other than urogenital development); alterations in their expression and activity have been associated with metabolic disease, polycystic ovarian syndrome, inflammation and bone metabolism. This review will outline the evidence base for the extra-urogenital role of 5-reductases from *in vitro* cell systems, pre-clinical models and human studies, and highlight the potential adverse effects of 5αR inhibition in human health and disease.

1. Steroid hormones and pre-receptor steroid hormone metabolism

Steroid hormones, including glucocorticoids (GCs), androgens and oestrogens, are synthesised within the adrenal glands and gonads and play a crucial role in embryonic development, cellular differentiation and metabolic homeostasis [1]. They exert a wide variety of effects in the body across almost all tissues. Steroid hormones are fat-soluble molecules and, *via* the circulation, pass through the cell membrane and bind to cytoplasmic or nuclear steroid hormone receptors. The potent impact of steroid hormones is demonstrated by states of excess and deficiency. As examples, androgen deficiency in men and oestrogen deficiency in women are associated with adverse metabolic features, including insulin resistance and decreased bone mineral density [2–4]. GC excess is associated with central obesity, hypertension, hyperlipidemia and glucose intolerance, whilst glucocorticoid deficiency, as a result of adrenal or pituitary pathology, can lead to life threating crisis characterised by hypotension and electrolyte abnormalities [5,6].

However, availability of these hormones to bind to their receptors is not only dependent on circulating levels, but also tightly controlled by the expression and activity of a series of enzymes that are able to metabolise steroid hormones before binding to their cognate receptors, in so-called 'pre-receptor metabolism'. With regards to GCs, the roles of the isoforms of 11β-hydroxysteroid dehydrogenase (11βHSD, type 1 and 2), which interconvert inactive cortisone and active cortisol, are well described, and their activity has been implicated in the pathogenesis of many aspects of health and disease including obesity, insulin resistance, hypertension and fetal development [7–13]. The 5-reductases (5α-reductase type 1 and 2 [5αR1 and 2] and 5β-reductase [5βR]) have a role to clear GCs but, in addition, have broad substrate specificity and, therefore, the potential to regulate the availability of several classes of steroid hormones [14] (Fig. 1). 5αR2 has an established role in male sexual development (in which it activates testosterone to the more potent 5α-dihydrotestosterone [5αDHT]), with inactivating mutations leading to 46XY Disorder of Sexual Development (DSD) [15,16]. However, there is now increasing evidence to suggest that altered 5-reductase activity and expression can impact upon other aspects of health and disease, along-with their established role in urogenital development

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or regulating androgen availability, for example in the context of prostate enlargement and malignancy. The current review will focus on the extra-urogenital role of these enzymes, and will try to describe the advancements from *in vitro*, *in vivo* and human studies.

2. 5α-reductases

2.1. Type 1 and 2 5αR gene structure and protein properties

The 5αR enzyme was first isolated from rat liver homogenates in the 1950s [17] but, due to high protein insolubility, it was not until the late 1980s when the first human 5αR isozyme was identified. Rat liver cDNA encoding 5αR was initially isolated from Xenopus laevis oocytes by expression cloning, and was then used as a hybridisation probe to screen a human prostate cDNA library [18]. The human 5αR protein encoded by this cDNA, however, demonstrated distinct biochemical properties and different pH optimum, compared to previous studies that had already described 5αR activity [18]. Further work revealed that this gene was normal in patients with genetic steroid 5αR deficiency [19], an observation that led to the hypothesis that two different 5αR isozymes exist. One year later, Andersson et al. [20] demonstrated the presence of two functional 5αR enzymes in humans, 5αR1 and 2.

The gene encoding 5αR1 (*SRD5A1*) is located on chromosome 5, consists of 5 exons and is expressed in liver, skin, scalp, bone and prostate, ovaries, and adipose tissue. The enzyme encoded by this gene is a hydrophobic protein with a molecular weight of 29 kDa [21] and has a broad pH optimum (6.0–8.5). The gene encoding 5αR2 (*SRD5A2*) is located on chromosome 2 and consists of 5 exons. 5αR2 is also a hydrophobic protein with a molecular weight of 28 kDa, shares less than 50 % homology with 5αR1 and has a narrow acidic pH optimum (5–5.5). Both isoforms use reduced nicotinamide adenine dinucleotide phosphate (NADPH) as a hydride donor co-factor and are responsible for the conversion of testosterone to 5αDHT; however, 5αR1 has a lower substrate affinity for testosterone (K_m = 1–5 uM), compared to 5αR2 (K_m = 0.004–1 uM) [22]. 5αRs also inactivate cortisol to 5α-dihydrocortisol, which is then converted, in a non-rate limiting step, to its tetrahydro-metabolite, 5α-tetrahydrocortisol (5αTHF), by the 3α-hydroxysteroid dehydrogenases AKR1C1, -C2, -C3 and -C4 [23–25]. Nonetheless, 5αRs have a lower affinity towards cortisol compared to testosterone [18]. Beyond testosterone and cortisol reduction, 5αRs convert progesterone, androstenedione, epitestosterone, aldosterone and deoxycorticosterone to their 5α-reduced metabolites. 5αR proteins are conserved in all primary eukaryotes sharing similar biological functions [26]. However, findings in pre-clinical compared with human studies are often contradictory, suggesting species-specific differences in 5αR activity. Such differences were exemplified by Thigpen et al. [27] who compared rat and human 5αR1 homologs: the two proteins shared 60 % amino acid identity, and demonstrated distinct sequence differences resulting in differential sensitivity to finasteride (a potent 5αR inhibitor that will be discussed in section 2.4.) Supporting this, in a more recent study [28], sequence alignment analysis of SRD5As revealed that, whilst the NADP-binding residues in 5αRs are highly conserved across different species, the finasteride-binding pocket residues are much less well conserved.

2.2. Tissue distribution

Both 5αR1 and 5αR2 are ubiquitously expressed in adult tissues, with highest levels of expression found in human liver and in male reproductive tissues, including the epididymis, prostate, seminal vesicles and genital skin [18,21,29,30]. Sexual dimorphism in 5αR activity exists, but data have been conflicting: human subcutaneous adipose tissue biopsies did not show any significant differences in 5αR1 mRNA expression between men and women [13]. However, Finken et al. [31] reported lower 5αR activity in young healthy females compared to males, as measured by lower urinary 5αTHF/cortisol ratios, and Tomlinson et al. [13] described higher absolute levels of urinary 5α-reduced metabolites in obese men compared to women. In contrast, both Fraser et al. [32] and Andrew et al. [33] observed higher 5αR activity in women, as measured by urinary THF/alloTHF and 5β/5αTHF ratios, respectively. This

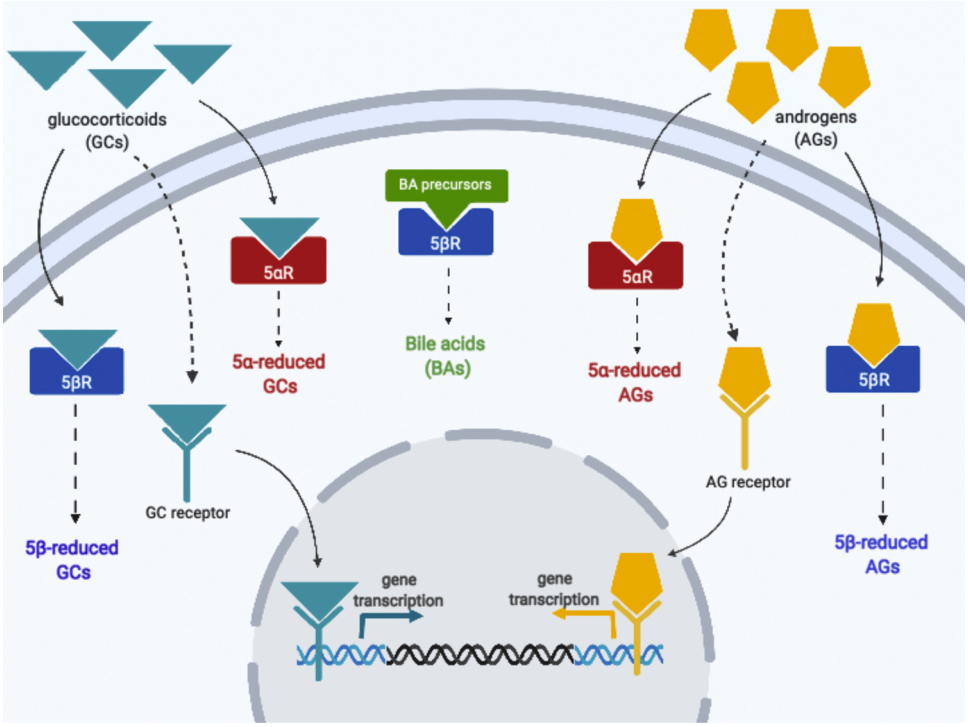

Fig. 1. The 5-reductases have a broad substrate specificity including the regulation of glucocorticoid (GC) and androgen (AG) receptor activation. 5α-reductase (5αR) type 1 and 2 convert GCs and AGs to their 5α-reduced metabolites. Similarly, 5β-reductase (5βR) converts GCs and AGs to 5β-reduced metabolites, but, in addition, catalyses the conversion of bile acid (BA) precursors towards the formation of primary BAs. Image created with BioRender.com.

discrepancy can be explained by the analysis of different urinary metabolite ratios, and this potentially reflects the limitations of the use of urinary steroid metabolome analysis. As an example, cortisol is metabolised by multiple enzymes (*e.g.*, 5αRs, 5βR, 11βHSDs) and urinary steroid ratios cannot always determine which component of the ratio drives alterations that reflect 5αR activity. mRNA and protein expression of 5αRs in human liver biopsies are helpful, but due to the invasive nature of the procedure, this is only feasible in specific circumstances.

A number of studies have reported alterations in 5αR tissue distribution during the different periods of life [22]. In 1993, Thigpen et al. revealed the presence of 5αR2 protein expression in fetal genital skin, as measured by immunoblotting [29]. A later study of Ellsworth and Harris [34] demonstrated 5αR1 as the predominant protein expressed in male and female fetal scalp and non-genital (back) skin tissues, with similar levels of activity between males and females. However, this was 20−50-times lower when compared to 5αR1 activity in adult skin. In addition, they demonstrated 5αR2 as the predominant protein expressed in fetal prostate, with 5αR2 activity levels similar to those seen in adult prostatic tissues. More recently, Lunacek [35] also identified detectable 5αR1 protein expression in fetal epithelial prostatic cells, suggestive of a role of this isoform in human prostate development. After birth, both 5αR1 and 5αR2 proteins have been found to be transiently expressed in newborn skin and scalp (until approx.1.5 years of age), and then permanently expressed from the time of puberty [29]. In contrast, expression of both isoforms (either mRNA or protein) have been detected in the prostate throughout postnatal life [22]. Finally, neither of the two proteins has been detected in fetal livers, but both are expressed in the liver after birth and throughout postnatal life [29].

2.3. Type 3 5αR gene structure and protein properties

In addition to 5αR1 and 5αR2, a third 5αR has been identified (*SRD5A3*, putative 5αR3) but the role of this enzyme is not entirely clear [36]. The gene encoding this isoform is located on chromosome 4 and consists of 6 exons. 5αR3 is found in a variety of human tissues, including the liver, skin, kidney, skeletal muscle, pancreas and testis, and is the mostly highly expressed 5αR isoenzyme in human abdominal adipose [37]. In addition, 5αR3 is found in malignant human tissue types (*e.g.*, prostate, testis, breast lung and thyroid cancer cells), suggestive of its role as a potential cancer biomarker [38]. A number of studies have tried to elucidate the role of this enzyme in steroid hormone metabolism, but data have been conflicting. In one study, 5αR3 over-expression in HEK293 cells catalysed the conversion of testosterone and androstenedione to their 5α-reduced metabolites [39]; in contrast, in another study using the same cell model, both human and hamster 5αR3 isoforms failed to metabolise testosterone, progesterone, androstenedione or corticosterone [40]. Recent evidence from clinical and experimental studies, however, suggest that this enzyme has an important role in the reduction of polyprenol to dolichol, and that mutations in *SRD5A3* result in congenital disorders of glycosylation. These mutations result in mental retardation and ophthalmologic and cerebellar atrophy, but have no effects on steroid metabolism [41–46].

2.4. 5αR inhibitors

The most widely used 5αR inhibitor in human studies has been finasteride, which selectively inhibits the activity of 5αR2, but not 5αR1 [47]. Finasteride is a synthetic, steroidal, 4-azasteroid compound and is extensively used clinically in the treatment of benign prostatic hyperplasia (BPH) and prostate cancer [48–51]. Although it was originally believed to act as a reversible competitive inhibitor, it was later found to be an irreversible, mechanism-based inhibitor of 5αR2 [18,51]. Dutasteride is another 4-azasteroid, steroidal 5αR inhibitor that inhibits all 5αR isoforms and, due to its broader inhibitory activity, has been shown to suppress serum DHT levels by $>$ 90 % compared to the 70 % seen with finasteride in patients with BPH [52]. 4-azasteroids are the most well studied inhibitors of 5αR and, apart from finasteride and dutasteride, 4-MA, turosteride, MK-386, MK-434 and MK-963 have also been described. 4-MA is an anti-androgen with a dual action, potently inhibiting both 5αR1 and 2, as well as acting as a poor antagonist for the androgen receptor (AR) [53]. A recent *in vitro* study demonstrated an ability for both 4-MA and finasteride to inhibit 5αR3 activity in adipose cells [37]. However, 4-MA is now withdrawn from clinical practice due to hepatotoxic side effects [54]. Whilst MK-386 is a selective 5αR1 inhibitor, turosteride, MK-434 and MK-963 predominantly inhibit 5αR2 [55]. Other steroidal 5αR inhibitors include 6-azasteroids (*e.g.* GI1S7669X), 10-azasteroids (*e.g.* AS97004), androstanecarboxylic acids and progesterone esters [54–57]. In addition to steroidal inhibitors, a number of non-steroidal 5αR inhibitors have also been introduced, including benzo[f]quinolinones, pyridones and quinolinones [54]. The impact of these inhibitors to regulate aspects of health and disease unrelated to their role in the treatment of prostate disease has only been examined in a very small number of studies and these will be discussed in the relevant sections below.

2.5. 5αR in adipose tissue

5αR1 and 5αR3, but not 5αR2, mRNA and protein expression have been detected in human male omental and subcutaneous adipose tissues, and mRNA expression in male omental and subcutaneous preadipocytes, suggesting an intracrine role for 5αRs in adipose steroid metabolism [37]. 5αR1 mRNA expression have also been detected in female subcutaneous adipose tissue, but no differences in mRNA expression were observed between males and females [13]. Although, in general, studies report lack of 5αR2 expression in adipose tissue [37,58,59], a single study has demonstrated significant 5αR2 mRNA expression in female omental and subcutaneous adipose [60], indicative of potential sex-specific differences in 5αR expression and activity in fat. Androgens, including testosterone and 5αDHT, inhibit adipocyte differentiation [61, 62], however, the role of 5αRs in adipose tissue is still poorly understood. In a recent *in vitro* study [37], testosterone and androstenedione treatment (both 5αDHT precursors) of subcutaneous preadipocytes inhibited preadipocyte differentiation, and this effect was reversed following treatment with both finasteride and 4-MA, suggestive of a direct role of 5αRs in adipocyte differentiation. 5αRs also seem to play a role in the metabolism of other steroids in adipose tissue; a study has reported 5α-pregnane-3α/β-ol-20-one, 5α-pregnanedione and 5α-pregnane-20α-ol-3-one as the major metabolites of progesterone in omental and subcutaneous preadipocyte cultures [63]. The broader metabolic effects of 5αR activity on adipose tissue will be further discussed below.

2.6. 5αR and metabolic syndrome

The term metabolic syndrome is used to describe a cluster of conditions including obesity, dyslipidaemia, hypertension and fasting or post-prandial hyperglycaemia that, in combination, are associated with a significant increased risk of cardiovascular morbidity and mortality. There are relatively few *in vitro* studies that have examined the role of 5αR in the regulation metabolic phenotype. In rat hepatocytes, pituitary hormones, androgens, glucocorticoids and insulin have been reported to affect 5αR1 mRNA expression and 5αR activity. In both human and rat skin fibroblasts, androgens induce skin 5αR activity, an effect that seems to be controlled by insulin-like growth factor 1 (IGF-I) [64–66]. More recently, in human primary hepatocyte models, Nasiri et al. [67] demonstrated that the ability of cortisol to limit lipogenesis (in the absence of insulin) was potently regulated by 5αR2 activity. Over-expression of functionally active 5αR2, enhanced cortisol removal and therefore limited the ability of cortisol to inhibit lipogenesis. In contrast, 5αR inhibition, using either finasteride or dutasteride, augmented the actions of cortisol.

Rodent studies have further developed our understanding of the role of 5αRs in metabolic tissues. Hepatic 5αR1 mRNA and protein levels are

increased in obese Zucker rats when compared to lean animals [68]. However, in a further study, no differences in hepatic and omental fat 5αR1 mRNA expression between control and high-fat diet Wistar rats were observed [69]. The reason for this difference remains unclear, but may reflect the different aetiology of obesity as well as the different genetic backgrounds of the two rat models [70]. Mice with global deletion of 5αR1 have also been generated and their metabolic phenotype has been explored in a small number of studies [71,72]. When extrapolating the findings of these studies, it is important to note the lack of expression of 5αR2 in rodent liver, contrasting with human liver where both 5αR1 and 5αR2 are highly expressed. 5αR1 KO mice developed increased hepatic TAG accumulation after feeding with the American lifestyle-induced obesity syndrome diet (ALIOS) [71]. As expected, the ALIOS diet did not have an impact of hepatic TAG levels in 5αR2 KO mice. Extending these findings, genetic deletion of 5αR1 was associated with insulin resistance (as measured through insulin secretion in response to intra-peritoneal glucose loading) on both normal chow and a high fat diet. In addition, using a carbon tetrachloride injury model, 5αR1 KO were more susceptible to the development of hepatic fibrosis [72].

Results from observational clinical studies measuring urinary steroid concentrations, using gas-chromatography-mass spectrometry (GC–MS) analysis, revealed an association between enhanced 5αR activity in obese men and women, increased BMI and increased insulin resistance [13,33,73,74] which decreases with significant weight loss [73]. Elevated levels of 5α-reduced cortisol metabolites have also been observed in male patients with type 2 diabetes mellitus (T2DM) and have also been linked to steatosis and non-alcoholic steatohepatitis (NASH) [75,76]. In agreement with these data, increased cortisol clearance measured by isotope clearance using liquid chromatography-mass spectrometry correlated with hepatic steatosis and insulin resistance in men [77]. Dowman et al. [71] demonstrated increased 5αR1, but not 5αR2, hepatic protein expression in NASH patients, however, a study from Westerbacka et al. [78] reported a decreased proportion of cortisol metabolised by 5αR with increasing levels of hepatic steatosis. Finally, a study from Ahmed et al. [79] showed a switch in liver cortisol metabolism across the NAFLD spectrum, with increased 5αR activity in patients with steatosis but with decreased mRNA expression of 5αR2 in explant livers with NASH, compared to controls. In total, these studies highlight the important pre-receptor role of 5αRs in regulating glucocorticoid availability, and changes in 5αR activity may serve as a protective mechanism to limit the adverse metabolic effects of glucocorticoids during the early stages of NAFLD, and maximise their anti-inflammatory properties as the disease progresses.

There have been relatively few interventional clinical studies published. Weight loss using lifestyle interventions, very low calorie diets or bariatric surgery have been associated with decreased 5αR activity, as measured by 5α-reduced cortisol metabolites [73,80–82]. Until very recently, the metabolic impact of 5αR inhibitors had not been examined. A single study by Upreti et al. [58] demonstrated that dutasteride, but not finasteride, modulated insulin sensitivity by reducing insulin-stimulated glucose disposal and non-esterified fatty acid suppression in human peripheral tissues as well as increasing fat mass. Looking more closely at the impact of 5αR inhibitors upon the liver and adipose tissue, Hazlehurst et al. [83] showed that dual 5αR inhibition using dutasteride resulted in hepatic insulin resistance and hepatic lipid accumulation, as measured by magnetic resonance spectroscopy, with increased rates of *de novo* lipogenesis and decreased adipose tissue fatty acid mobilisation; however, finasteride was without effect. More recently, a study by Othonos et al. [84] demonstrated that 5αR inhibitors co-administered with prednisolone exacerbated the adverse metabolic effects of glucocorticoid treatment, impairing hepatic and adipose tissue insulin sensitivity as well as increasing peripheral insulin resistance and decreasing glucose oxidation. Specifically with regards to BPH now, one study reported increased blood glucose and HbA1c as well as elevated total cholesterol and low density lipoprotein concentrations following long-term dutasteride treatment in patients with BPH [85]. Consistent with these findings, a population based cohort study from Wei et al. [86] revealed increased evidence of onset T2DM in patients with BPH receiving 5αR inhibitors. Taken together, these studies highlight the potential adverse metabolic effects of 5αR inhibition and stress the careful consideration of prescribing 5αR inhibitors alone or combined with synthetic glucocorticoids in men with BPH.

Advanced scarring and fibrosis of the liver predisposes to an increased risk of development of hepatocellular carcinoma (HCC). Although not significant, a low-activity genotype polymorphism in the *SRD5A2* gene has been reported to be associated with increased risk of HCC [87], whilst, another study revealed increased methylation of *SRD5A2* in liver cancer compared to non-tumor liver tissues [88]. In animal studies, however, genetic deletion of 5αR1 protected male mice against liver cancer [71], and pharmacological 5αR inhibition using the 5αR inhibitor FK143 suppressed the formation of HCC in male Fischer rats [89]. In total, these studies indicate a potential role of steroids, in particular cortisol and DHT, in hepatocellular carcinoma, but further work examining the prolonged effects of 5αR in cortisol and/or DHT availability in the context of liver cancer is needed.

2.7. 5αR and polycystic ovarian syndrome (PCOS)

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders with estimates that it may affect up to 10 % of the female population [90]. It is characterised by clinical and biochemical androgen excess and is often associated with metabolic dysfunction that may include insulin resistance with glucose intolerance, central obesity, dyslipidaemia and NAFLD [91–94].

Due to their role in active androgen generation, the 5αRs have been extensively investigated to determine a putative role in driving the PCOS phenotype. Several studies have reported an association between genetic variants of 5αRs and PCOS. A study from Goodarzi et al. [95] on obese, hyperandrogenic women, demonstrated seven single-nucleotide polymorphisms (SNPs) in the *SRD5A1* gene that were associated with both PCOS and hirsutism. Characterisation of eight more SNPs in *SRD5A2*, however, revealed an association of this isoform with PCOS, only [95]. Extending this work, characterisation of the same polymorphisms in lean women with PCOS showed a similar association between *SRD5A1* and *SRD5A2* variants and PCOS [96].

A number of studies *in vitro* have tried to elucidate the role of 5αR in PCOS. Detailed work from Jakimiuk et al. [97] demonstrated the presence of 5αR1 and 2 mRNA expression in granulosa and, to a lesser extent, in thecal cells, in both healthy women and women with PCOS. Although no differences in granulosa 5αR1 or 2 mRNA expression were observed between healthy and PCOS subjects, both 5αR1 and 2 mRNA expression were lower in PCOS thecal follicles, compared to controls. In this study, protein expression was not measured, and cell based kinetic analysis revealed a 4-fold higher 5αR activity in PCOS follicles than in controls. It should, however, be noted that the 5αR isoforms demonstrate different pH optima (5αR1 has a broad, slightly basic pH optimum and 5αR2 a narrow acidic optimum) but, due to the limited amount of available follicular tissue, 5αR activity assays were performed at physiological pH. It is therefore possible that the observed effects in 5αR activity may not accurately reflect the *in vivo* conditions [97]. Endorsing these data, a later study demonstrated increased 5αR1 and 2 activity in dermal fibroblasts (isolated from pubic skin) from patients with PCOS, compared to healthy women [98].

Several studies have assessed global 5αR activity through measurement of urinary steroid metabolites, but results have been conflicting. Some have revealed enhanced 5αR activity in patients with PCOS compared to healthy controls [99–103], with evidence suggestive of increased 5αR activity in daughters of PCOS women during early childhood, as measured by higher 24 -h urinary 5αTHF/THF ratios, compared to control girls [104]. However, other studies have reported

no differences in enzyme activity between PCOS and controls [105–107]. It is possible that discrepancies between different studies are the result of different sample sizes used or the confounding effects of the metabolic abnormalities associated with PCOS. In addition, and as mentioned above (see section 2.2), urinary steroid ratios come with limitations, as they are often based on pairing 5α- and 5β-reduced metabolites or measuring substrate/product ratios; therefore, any differences between groups could denote changes in either of the components, thus making it difficult to directly equate these data with 5αR activity. A recent meta-analysis, where all the relevant studies were included, demonstrated increased 5αR activity in PCOS subjects compared with BMI-matched controls, as well as an association between increased enzyme activity in PCOS and insulin resistance [108].

Despite the apparently critical role of 5αR activity in the pathogenesis of PCOS, the potential effect of 5αR inhibition in the PCOS-related metabolic phenotype is poorly described. A recent study by Wu et al. demonstrated increased muscle 5αR1 protein expression in PCOS rats, but no improvements in glucose or lipid metabolism following either 5αR1 or 5αR2 inhibition - using dutasteride and finasteride, respectively - were observed [109]. Endorsing these data, a later study from the same group revealed no improvements in insulin resistance in finasteride-treated PCOS rats [109,110]. However, as there are distinct differences in finasteride sensitivity between the human and the rat 5αR1 homologs (see section 2.2.), potential limitations in using rat models to study 5αR inhibition (due to species-specific differences) cannot be excluded.

Only a small number of studies have evaluated the potential therapeutic impact of finasteride in patients with PCOS and most have focused on the androgen related effects, notably hirsutism and ovarian function [110–114]. A single study from Diri et al. [115] explored the metabolic impact of finasteride in patients with PCOS, suggesting improvements in insulin resistance (HOMA-IR, AUC-glucose, AUC-insulin) after 12 months of finasteride treatment. These data, however, come in contrast with the previously mentioned studies in which dual 5αR inhibition by dutasteride resulted in elevated glucose levels and insulin resistance. Sex-specific differences as well as different aetiology may account for these conflicting observations: as 5αRs are critical for both glucocorticoid clearance and androgen formation, dual 5αR inhibition may result in glucocorticoid excess with concomitant adverse effects in insulin sensitivity. In patients with PCOS, however, finasteride possibly acts as an anti-androgenic agent, impairing androgen action and downstream improving insulin resistance. Supporting this hypothesis, additional clinical studies using other anti-androgenic agents, including flutamide and spironolactone, have also shown improved insulin resistance parameters in women with PCOS [116,117]. Despite these differences, 5αR inhibition could still serve as an effective treatment against both hyperandrogenemia and insulin resistance, the two major pathophysiological derangements in PCOS, but more clinical studies are needed.

2.8. 5αR and bone

Steroid hormones, notably androgens, oestrogens and GCs are potent regulators of bone physiology and pathology. In patients with endogenous hypercortisolism (Cushing's syndrome) as well as in people treated with GCs therapeutically (*e.g.*, rheumatoid arthritis), long-term GC exposure has been associated with adverse effects in bone health, including loss of bone density, deterioration of bone structure and increased fracture risk [118]. In contrast, oestrogens play a protective role in bone health in both sexes; they are needed during bone growth [119], and decline in oestrogen levels has been associated with trabecular and cortical bone loss in menopause women [120]. Additionally, androgen deficiency in hypogonadal men has been linked to lower bone mineral density, and these patients are at increased risk for osteoporosis and bone fractures [121].

Historical data suggest that 5αDHT is actively synthesised in human spongiosa bone tissue and that this is likely to be the predominant androgen acting in bone tissues [122]. Indeed, later studies revealed 5αR expression and activity in human bone and cultured human osteoblast-like cells (hOB cells). 5αR1 is the predominant isoform expressed in this cell type, with testosterone and androstenedione serving as substrates to generate 5α-androstanes [122–124]. 5αR expression has also been reported in human mesenchymal bone marrow cells. Dutasteride treatment inhibited the conversion of testosterone to 5αDHT in these cells, but the functional consequences of this upon cellular phenotype have not been explored [125].

In rodents, a small number of studies have investigated the role of 5αR in bone health by either genetically ablating 5αR or *via* pharmacological inhibition using finasteride. Bone development and density remained unaffected by finasteride treatment compared to untreated controls, reflecting the limited role of 5αR2 in bone and endorsing previous *in vitro* data [126]. More recently, 5αR1 KO male mice were shown to have reduced bone mass, with reduced trabecular bone mineral density and cortical bone mineral content, but no differences in androgen concentrations, compared to wild type animals [127]. In contrast, 5αR1 KO female mice displayed increased cortical bone mass and increased circulating androgen levels, potentially explaining the sex-specific differences in bone phenotype between the two models [127]. Taken together, these studies suggest that 5αR1 is the predominant functionally active and relevant isoform expressed in bone in humans and rodents.

Several clinical studies have examined the potential role of 5αR in bone through 5αR inhibition using finasteride and dutasteride. Prolonged treatment of patients with BPH with finasteride did not alter bone density [128–132]. In line with these data, there was no significant reduction in bone mineral density in patients with inactivating mutations in *SRD5A2* when compared to healthy controls, suggesting that conversion of testosterone to DHT by 5αR1 is sufficient to preserve bone health [133]. In addition, exogenous testosterone treatment combined with finasteride had no adverse effect on bone mineral density or bone loss. These data would suggest that either 5αDHT is not required for the beneficial effects of androgens in bone tissue or that 5αR1 is the most important isoform in bone [134–136]. Consistent with these findings, two independent studies have reported no association between increased fracture risk and pharmacological 5αR inhibition in older men, although there was a small increase risk of fractures in past users [137,138]. Furthermore, studies have demonstrated increased bone density following long-term inhibition of 5αR using dutasteride [132,139]. It is possible that, whilst finasteride treatment demonstrates no significant alterations in bone homeostasis, dual 5αR inhibition beneficially affects bone health, potentially due to redirection of testosterone metabolism towards oestrogen formation *via* aromatisation. Indeed, pre-clinical studies using male rats have reported reductions in bone mineral density and bone mass following either genetic or pharmacological aromatase inhibition [140,141], whilst, a clinical study demonstrated that androgen deficiency was associated with bone loss partially due to reduced testosterone-derived (*via* aromatisation) oestrogens in old men [142]. Of note, a relatively small population-based nested case-control study reported increased risk of osteoporosis in patients with BPH receiving finasteride treatment [143]. Considering that 5αR1 is the predominant form in bone, this deleterious effect of finasteride is rather confusing. An *in vitro* study has revealed the presence of an aromatase-independent pathway of testosterone conversion into oestrogenic steroids, which is inhibited by finasteride [144]; it is, therefore, possible that finasteride plays an additional role in oestrogen synthesis, potentially explaining the adverse effects observed in the above study. Taken together, 5αR inhibition does not appear to play a detrimental role in modulating bone homeostasis in healthy men, but careful consideration should be taken with regards to risk of osteoporosis in men with BPH.

2.9. 5αR and inflammation

Endogenous GC production increases in response to stress and has an important role in the regulation of inflammation. Indeed, the majority of therapeutic indications for GC use are reliant upon their anti-inflammatory actions. In addition, there is increasing evidence suggesting that androgens (especially testosterone and DHT) can act as modulators of inflammation in men [145]. Considering the crucial role of 5αRs in the regulation of steroid hormone availability (both GCs and androgens), a number of studies have focused on the potential of these enzymes to regulate inflammatory response in cellular models as well as in animal and human studies.

McInnes et al. [146] showed that the tetrahydro-metabolites of corticosterone (5αTHB) activated the hepatic GC receptor both *in vitro* and *in vivo*. In order to try to dissociate the inflammatory from the metabolic effects of GCs, in another study [147], both mouse bone marrow derived macrophages and male C57Bl/6 mice were treated with 5αTHB. The data revealed impaired LPS-induced secretion of the pro-inflammatory cytokines (TNF-α and IL-6) *in vitro* and *in vivo*, and increased secretion of the anti-inflammatory cytokine IL-10 *in vitro*, suggesting a role for 5α-reduced GCs as safer anti-inflammatory drugs, with potentially fewer adverse effects. However, these studies were performed only in rodents, in which corticosterone (but not cortisol) is the principal active glucocorticoid. Further work, investigating 5αTHF activity in human cell systems, would elucidate whether tetrahydro-metabolites of cortisol possess a similar anti-inflammatory role in humans.

Androgens are also able to regulate the inflammatory response although there is a clear tissue-specificity of response. For example, testosterone inhibits IL-1 production in murine macrophages and IL-6 production in human peripheral blood monocytes [148,149], and DHT reduces IL-6 expression in osteoblasts [150]. In contrast, testosterone increases the secretion of IL-6 and TNFα in chondrocytes and macrophages respectively [151,152]. In patients with BPH (which is associated with elevated NF-κB activity), increased prostate SRD5A2 expression has been positively correlated with disease severity [153]. Endorsing these data, in benign human prostate cell lines, chronic NF-κB activation induced *SRD5A* expression, most notably *SRD5A2* [153], indicative of increased DHT formation in this tissue. In this regard, in another *in vitro* study, 5αDHT treatment on stromal cell cultures derived from patients with BPH exerted a broad anti-inflammatory effect, inhibiting NF-κB activation and suppressing secretion of inflammatory markers, including IL-6 and IL-8 [154]. It is therefore possible that upregulation of SRD5A expression in prostate tissues acts as a compensatory mechanism, increasing prostate 5αDHT levels to limit the inflammatory response.

Inhibition of 5αR by MK-434 (a selective 5αR2 inhibitor) decreased inflammatory cell numbers and accelerated wound healing in male rats, suggesting a potential role of 5αR antagonism in wound healing [155]. In agreement with this, chronic pre-treatment of male Wistar rats with finasteride limited the inflammation associated with a formalin-induced foot paw oedema test [156].

5αR isoforms may also have a role in NASH (see section 2.3 above). Immunohistochemical analysis has suggested increased 5αR1 with increasing inflammation, with a concomitant decrease in 5αR2 gene expression [79]. Global activity as measured by urinary steroid metabolites has suggested decreased 5αR activity in NASH when compared with simple steatosis but was not different to healthy controls. It has been postulated that this decrease would enhance GC availability in an attempt to suppress local inflammation within the liver. Importantly, these studies performed in the context of NAFLD have only been conducted in very small numbers of patients and larger studies with accurately staged liver disease are needed before any firm conclusions can be drawn.

3. 5β-reductase (5βR)

3.1. 5βR gene structure and protein properties

5β-reductase (5βR) is a member of the aldo-keto-reductase (AKR) superfamily 1 of enzymes and is the first member of the 1D subfamily (AKR1D1), along with the rat (AKR1D2) and the rabbit (AKR1D3) 5β-reductase homologs [157,158]. The gene is located on chromosome 7 in humans [159], whilst in mice and rats is located on chromosomes 6 and 4 respectively. The full-length human gene consists of 9 exons and 8 introns (ENST00000242375.7, *AKR1D1−002*), and six splice variants have been identified, three of which are predicted to lead to functional protein isoforms: *AKR1D1−001* (NM_001190906), *AKR1D1−006* (NM_001190907), and *AKR1D1−002* (NM_005989) (Fig. 2) [160]. The full-length isoform (AKR1D1−002) encoded by this gene has a molecular weight of 37 kDa, consists of 326 amino acids and includes all 9 exons. It utilises NADPH as an electron donor and, although most aldo-keto reductases (AKRs) catalyse a reversible oxido-reduction, 5βR catalyses a stereospecific irreversible double bond reduction between the 4th and the 5th carbon of the A-ring of steroids [161]. The splice variants *AKR1D1−001* and *AKR1D1−006* are also translated to proteins with a molecular weight of ~37 kDa, however, they demonstrate distinct gene structures: *AKR1D1−001* lacks exon 5 resulting in a shorter 285 amino acid protein, whilst *AKR1D1−006* omits exon 8 and translates into a 290 amino acid protein [160,162].

5βR has an important pre-receptor role in the regulation of steroid hormone action, as it generates all 5β-reduced dihydrosteroid metabolites for C19-C27 steroids [159]. Both cortisol and cortisone are metabolised to 5β-dihydrocortisol and 5β-dihydrocortisone respectively by 5βR, and are then subsequently converted, in a non-rate limiting step, to their tetrahydro-metabolites (tetrahydrocortisol [5βTHF], and tetrahydrocortisone [5βTHE]) by 3αHSDs (Fig. 3). 5β-reduced glucocorticoids are unable to bind the glucocorticoid receptor and are largely considered inactive [146,163]. 5βR also inactivates progesterone (through multiple steps involving 3- and 20-HSD activities) to 5β-pregnane-320-diol as well as testosterone and 11-ketotestosterone to 5βDHT and 11K-5βDHT, respectively [164] (Fig. 3). Moreover, it inactivates aldosterone and its precursor corticosterone. Further to endogenous steroid hormones, two *in vitro* studies have recently demonstrated the ability of the full-length isoform to inactivate, albeit poorly, the synthetic glucocorticoids prednisolone and dexamethasone, with concomitant decreases in glucocorticoid receptor activation. Additional effort to characterise the functional activity of the *AKR1D1−001* and *-006* splice variants *in vitro* revealed that the translated truncated 5βR isoforms can also metabolise dexamethasone poorly, but had no effect in either cortisol, prednisolone, testosterone or androstenedione clearance [162]. However, not all 5β-reduced metabolites are inactive [159]. 5βTHF has been shown to reduce intraocular pressure in human trabecular meshwork cell lines [165], whilst it also exerted antagonistic properties on the neurotransmitter receptor $GABA_A$ in rat cerebral cortical synaptoneurosomes [166]. 5β-androstanes, in particular 3α-hydroxy-5β-androstan-17-one (etiocholanolone), induce porphyrinogenesis in avian liver cell cultures [167]; in humans, they possess pyrogenic activity *in vitro* and stimulate a local inflammatory response, when injected intramuscularly [168,169]. Additionally, as they lack any androgenic effects, 5β-androstanes have been proposed as testosterone substitutes for the treatment of anaemia, especially in female and young patients [159]. Of particular interest are the 5β-reduced metabolites of progesterone (5β-pregnanes). Several studies have revealed the ability of these steroids to stimulate erythropoiesis in birds, rodent and primates [170–172], as well as erythroid progenitor cell growth in human cell models [173]. In addition, 5β-pregnanes, in particular 3α-hydroxy-5β-pregnan-20-one (pregnanolone), can act as potent neuroactive steroids modulating $GABA_A$ and N-methyl-D-aspartate receptor activity, downstream regulating normal brain function and development. However, and despite the presence of *AKR1D1* expression in the brain, it

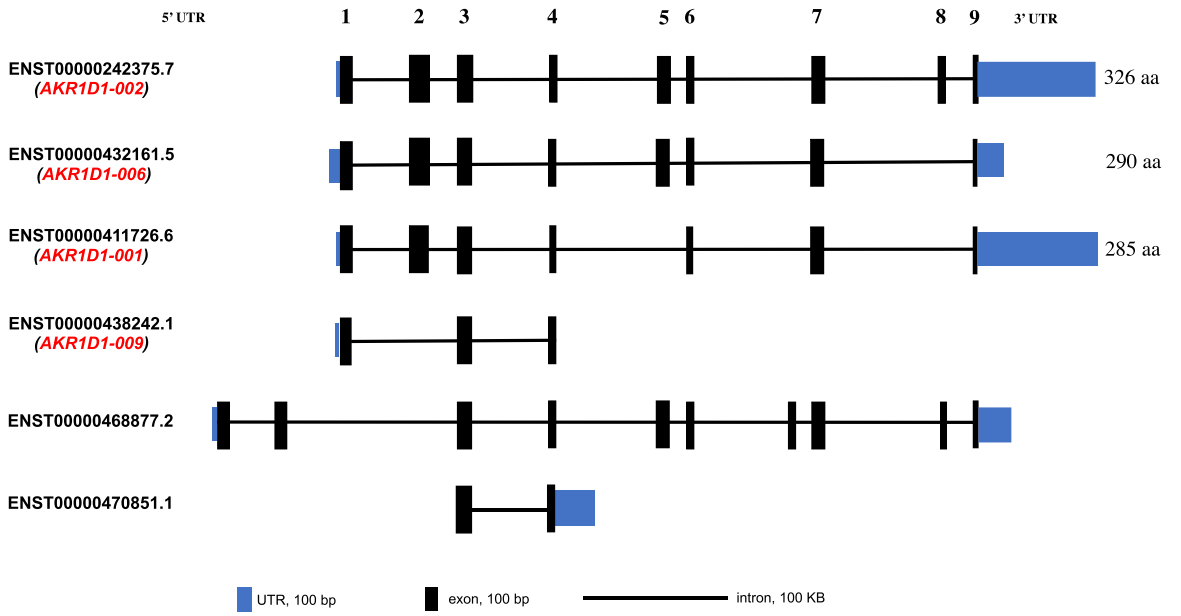

Fig. 2. Gene structure of 6 human *AKR1D1* splice variants. *AKR1D1-002*, *AKR1D1-006* and *AKR1D1-001* lead to functional proteins. Coding exons are in solid black boxes.

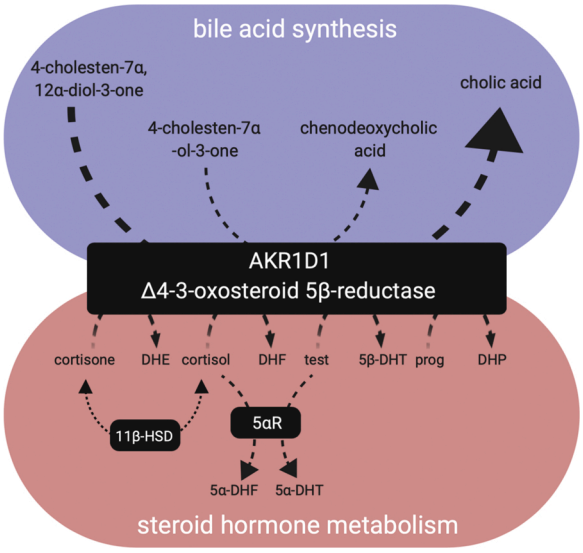

Fig. 3. The combined role for 5β-reductase in both bile acid synthesis and steroid hormone metabolism (DHE: dihydrocortisone; DHF: dihydrocortisol; DHT: dihydrotestosterone; prog: progesterone; DHP: dihydroprogesterone; 11β-HSD: 11β-hydroxysteroid dehydrogenase; 5αR: 5α-reductase). Image created with BioRender.com.

remains unknown whether *de novo* synthesis of 5β-pregnanes occurs in the central nervous system [159]. Further to their role in neurotransmission, 5β-pregnanes have been suggested to exert hepatic xenoprotective effects - by potently activating the liver pregnane-X- (PXR) and human constitutive-androstane- (CAR) receptors - as well as acting as potent tocolytic agents. More specifically, *in vitro* human work has reported inhibition of myometrial contraction by 5β-dihydroprogesterone, whilst reduced uterine *AKR1D1* expression and concurrent decreases in serum 5β-dihydroprogesterone levels have been correlated to the active phase of the first stage of human labour [174].

In addition to its role in steroid hormone clearance, 5βR has a crucial function in bile acid (BA) synthesis, using the intermediates 7α,12α-dihydroxy-4-cholesten-3-one and 7α,hydroxy-4-cholesten-3-one as substrates to catalyse the formation of cholic acid (CA) and chenodeoxycholic acid (CDCA) (Fig. 3) [175].

3.2. Tissue distribution

5βR is largely expressed in liver in humans (as in rats and mice), with levels in excess of 10-fold higher than any other tissue [159]. A number of studies have also reported the presence of 5β-reduced metabolites in foetal brain, uterus, testes and plasma, indicative of 5βR activity in these tissues [176,177]. Low levels of 5βR activity have also been found in testis, colon, skeletal muscle, adipose tissue and blood cells [63,175,178,179]. Although sex-related differences in 5βR have been reported in rats (and other animal species including mouse, fish, bird and frog [26,181,182]), with increased enzyme activity and cytosolic content in males compared to females [180], human data have been conflicting. Two independent studies have reported no sexual dimorphism in hepatic *AKR1D1* mRNA expression [183,184], however, Finken et al. [31] showed decreased urinary 5βTHF/cortisol ratios in menstrual females compared to males, suggestive of lower 5βR activity in women.

3.3. 5βR mutations

Since 1988, when the first evidence for defects in 5βR activity were reported by Clayton et al. [185] and Setchell et al. [186], a number of 5βR mutations have now been identified on different exons and are associated with severe cases of 5β-reductase deficiency. Among the characteristic biochemical findings, there are unusual ratios of primary bile acids, increased concentrations of total bile acids, hyper-3-oxo-Δ4 bile aciduria, increased aminotransferase and total bilirubin levels. In addition, disturbed glucocorticoid metabolism has been observed, with decreased and near total absence of 5β-reduced metabolites of corticosteroids [187,188]. These patients developed cholestasis, portal inflammation, fibrosis and jaundice [189–195]. Treatments with ursodeoxycholic acid (UDCA), chenodeoxycholic acid (CDCA) and cholic acid (CA) are effective. However, in some cases, liver function can continue to deteriorate necessitating liver transplantation [194]. Despite the potential severity of these cases, survival into adulthood in the absence of treatment is reported [188].

3.4. 5βR inhibitors

Although the utility of 5βR inhibition is yet to be justified and could be questioned bearing in mind the phenotype associated with mutations in 5βR, compounds have been developed and tested as selective inhibitors. 4-Chloromercuribenzoic acid (pCMB), a sulfhydryl organomercury compound that is used as a protease inhibitor, has the ability to inhibit 5βR activity (concentrations ranging from 0.01−0.1 mM), using androstenedione as a substrate [196]. Drury et al. [197] tested finasteride as a potential 5βR inhibitor, however, it only acted as a competitive inhibitor with low micromolar affinity (K_i = 2.1 μM), when testosterone was used as substrate. More recently, non-steroidal anti-inflammatory drugs (NSAIDs) that inhibit the human AKR1C1-C4 enzymes have been examined as potential 5βR inhibitors using testosterone as substrate, but they failed to inhibit enzyme activity. In the same study, the natural inhibitors of AKR1C2, CDCA and ursodeoxycholic acid were tested against 5βR; both acted as non-competitive inhibitors of 5βR activity (Ki = 3.2 μM and Ki = 9.8 μM for CDCA and ursodeoxycholic acid, respectively) [198].

3.5. Role of 5βR in metabolic syndrome

A limited number of studies have begun to explore the role of 5βR in the regulation of metabolic phenotype, using human *in vitro* as well as *in vivo* rodent and human models. *In vitro,* silencing of 5βR in human hepatoma cells regulates steroid hormone availability and primary bile acid synthesis [163,199]. Genetic depletion of 5βR increased intracellular TAG accumulation, inflammation, and impaired fatty acid oxidation. These effects were mediated through multiple nuclear receptor hormones, including the farnesoid-X and the liver-X receptors which are putatively activated by accumulation of oxysterol bile acid precursors [199,200] (Fig. 4). More recently, we have shown that 5βR expression and activity is regulated by synthetic GCs *in vitro* and *in vivo*, and that down-regulation of 5βR activity in human liver cell lines increases the expression of gene markers of gluconeogenesis and glycogen synthesis (in the absence of any glucocorticoid treatment), suggestive of an additional indirect role of GCs in regulating hepatic glucose metabolism, through modulation of bile acid synthesis [200].

In rodent models, obese Zucker rats have increased hepatic 5βR mRNA expression and 5βR activity and this was partially reversed following insulin sensitisation with metformin or rosiglitazone [68]. Whilst 5βR activity is not detectable in adipose tissue, increased 5βR mRNA expression and activity have also been observed in livers from obese mice compared to wild type animals [201]. Consistent with these studies, elevated hepatic 5βR activity was observed in Wistar rats following 3 weeks on a high-fat diet, however, this effect was lost after 20 weeks of high-fat feeding [69]. More recently, a 5βR-KO mouse model was developed revealing alterations in BA composition and synthesis. These 5βR-KO mice demonstrated a sexually dimorphic metabolic phenotype, with male, but not female, KO mice showing lower body weight gain, lower total fat mass and smaller subcutaneous adipose depots when fed on a normal chow diet for 30 weeks; additionally, both male and female KO mice had enhanced insulin sensitivity compared to their wild type littermates, but no changes in glucose tolerance [202].

In humans, data have been conflicting. A single study utilising the measurement of urinary steroid hormone metabolites has demonstrated an association between increased 5βR activity and hepatic steatosis [78]. Increased 5βR activity with enhanced cortisol clearance and a positive correlation between 5βR activity and insulin levels have also been reported in women with PCOS [106]. In contrast, elevated levels of 7α,hydroxy-4-cholesten-3-one, the bile acid precursor substrate for 5βR, was observed in patients with NAFLD [203]. In line with this, two more studies have recently demonstrated lower 5βR expression in patients with NAFLD and T2DM [199,204].

4. Conclusions and future directions

Steroid hormones, including GCs and androgens, regulate multiple aspects of health and disease, and there is now a rapidly growing body of evidence to implicate the 5-reductases in controlling phenotype outside their perceived traditional role to regulate androgen availability in urogenital tissues. The full translational potential of the 5-reductases is yet to be fully explored. Targeted inhibition appears to have a complex, sexually dimorphic impact reflecting their diverse array of substrates and enzymatic products. However, assessment of their activity may provide a tool to predict the future development of adverse metabolic consequences. Furthermore, given their role in the metabolism of exogenous steroids, determination of their activity may have the potential to predict the development of adverse side effects and ultimately aid dose selection and titration.

Disclosure summary

Nothing to declare.

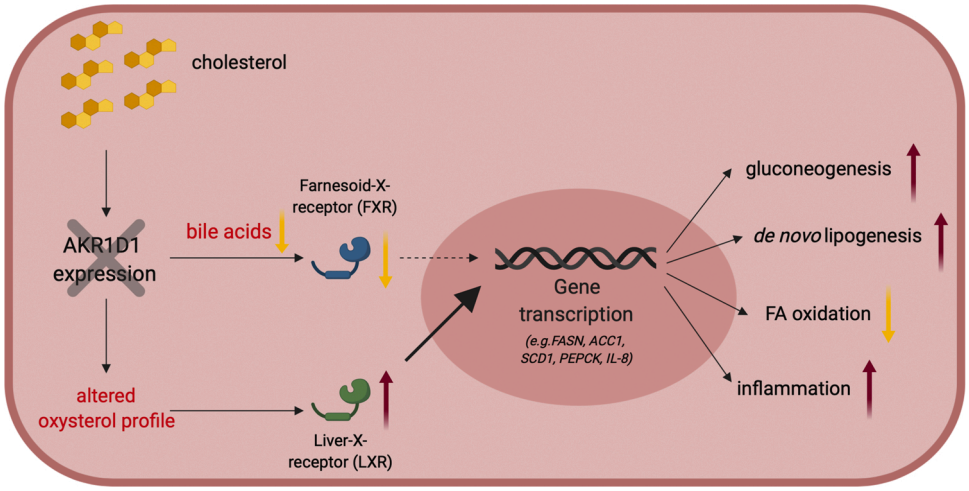

Fig. 4. Proposed mechanism of 5β-reductase activity in the regulation of hepatic metabolism. *AKR1D1* is predominantly expressed in hepatocytes. Impaired 5β-reductase (AKR1D1) activity has been shown to modulate farnesoid-X-receptor (FXR) and Liver-X-receptor (LXR activation), with downstream effects on hepatic gluconeogenesis, *de novo* lipogenesis, fatty acid (FA) oxidation and intracellular inflammation [199,200]. Image created with BioRender.com.

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CRediT authorship contribution statement

Nikolaos Nikolaou: Writing - original draft, Writing - review & editing. **Leanne Hodson:** Writing - review & editing, Supervision. **Jeremy W. Tomlinson:** Writing - review & editing, Supervision, Funding acquisition.

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