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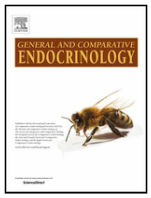

Consequences of steroid-5α-reductase deficiency and inhibition in vertebrates

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ABSTRACT

In 1974, a lack of 5α-dihydrotestosterone (5α-DHT), the most potent androgen across species except for fish, was shown to be the origin of a type of pseudohermaphrodism in which boys have female-like external genitalia. This human intersex condition is linked to a mutation in the steroid-5α-reductase type 2 (*SRD5α2*) gene, which usually produces an important enzyme capable of reducing the Δ^4-ene of steroid C-19 and C-21 into a 5α-stereoisomer. Seeing the potential of SRD5α2 as a target for androgen synthesis, pharmaceutical companies developed 5α-reductase inhibitors (5ARIs), such as finasteride (FIN) and dutasteride (DUT) to target SRD5α2 in benign prostatic hyperplasia and androgenic alopecia. In addition to human treatment, the development of 5ARIs also enabled further research of SRD5α functions. Therefore, this review details the morphological, physiological, and molecular effects of the lack of SRD5α activity induced by both SRD5α mutations and inhibitor exposures across species. More specifically, data highlights 1) the role of 5α-DHT in the development of male secondary sexual organs in vertebrates and sex determination in non-mammalian vertebrates, 2) the role of SRD5α1 in the synthesis of the neurosteroid allopregnanolone (ALLO) and 5α-androstane-3α,17β-diol (3α-diol), which are involved in anxiety and sexual behavior, respectively, and 3) the role of SRD5α3 in N-glycosylation. This review also features the lesser known functions of SRD5αs in steroid degradation in the uterus during pregnancy and glucocorticoid clearance in the liver. Additionally, the review describes the regulation of SRD5αs by the receptors of androgens, progesterone, estrogen, and thyroid hormones, as well as their differential DNA methylation. Factors known to be involved in their differential methylation are age, inflammation, and mental stimulation. Overall, this review helps shed light on the various essential functions of SRD5αs across species.

1. Introduction

In the 1950s, various case studies of men with pseudo-female external genitalia and enlarged clitorises were observed (Nowakowski and Lenz, 1961). These men exhibited a masculine body type, no breast, normal epididymis, deferent duct, and seminal vesicles. This condition was thought to originate from a single gene mutation (Nowakowski and Lenz, 1961). The condition was classified as pseudovaginal perineoscrotal hypospadias. A few years later, a small population of men exhibiting external genitalia ambiguity at young age was also described. The men were raised as girls and when they reached puberty, the men showed signs of virilisation, such as deepening of the voice and an increase in muscle mass (Imperato-McGinley et al., 1974). Like the cases from the 1950s, they also had normal epididymis and vas deferens, as well as testes showing signs of functional spermatogenesis. Imperato-McGinley et al. (1974) showed the condition was linked to a decrease in production of 5α-dihydrotestosterone (5α-DHT). 5α-DHT has a higher affinity for the androgen receptor (AR) than testosterone (T) (Deslypere et al., 1992), except in fish in which 11-ketotestosterone (11KT) is the more potent androgen (Martyniuk et al., 2013). This decline in 5α-DHT's production in those men is now known to be linked to a deficiency in steroid-5α-reductase type 2 (SRD5α2), which reduces T into 5α-DHT.

SRD5α2 is part of the SRD5α enzyme family, which has the ability to reduce the Δ^4-ene of steroid C-19 and C-21 into a 5α-stereoisomer (Fig. 1A) and are NADPH-dependent oxidoreductase (Russell and Wilson, 1994). There are five members of the SRD5α family: SRD5α1, SRD5α2, SRD5α3, glycoprotein synaptic 2 (GSPN2), and GSPN2-like, as shown by phylogenetic analysis (Cantagrel et al., 2010; Langlois et al., 2010a). SRD5αs are bound to endoplasmic reticulum membrane (Liang et al., 1985; Yokoi et al., 1996; Cantagrel et al., 2010; Scaglione et al., 2017), which can be explained by the predicted α-helices in their structure (Bhattacharjee et al., 2011; Jayadeepa and Sharma, 2011; Shamsara, 2018). Even though SRD5αs can perform the same reaction, they are expressed differently in the body (Table 1) and exert different functions: SRD5α1 is mainly linked to the production of neurosteroids, such as allopregnanolone (ALLO), which can decrease anxiety (Darbra and Pallarès, 2010; Darbra et

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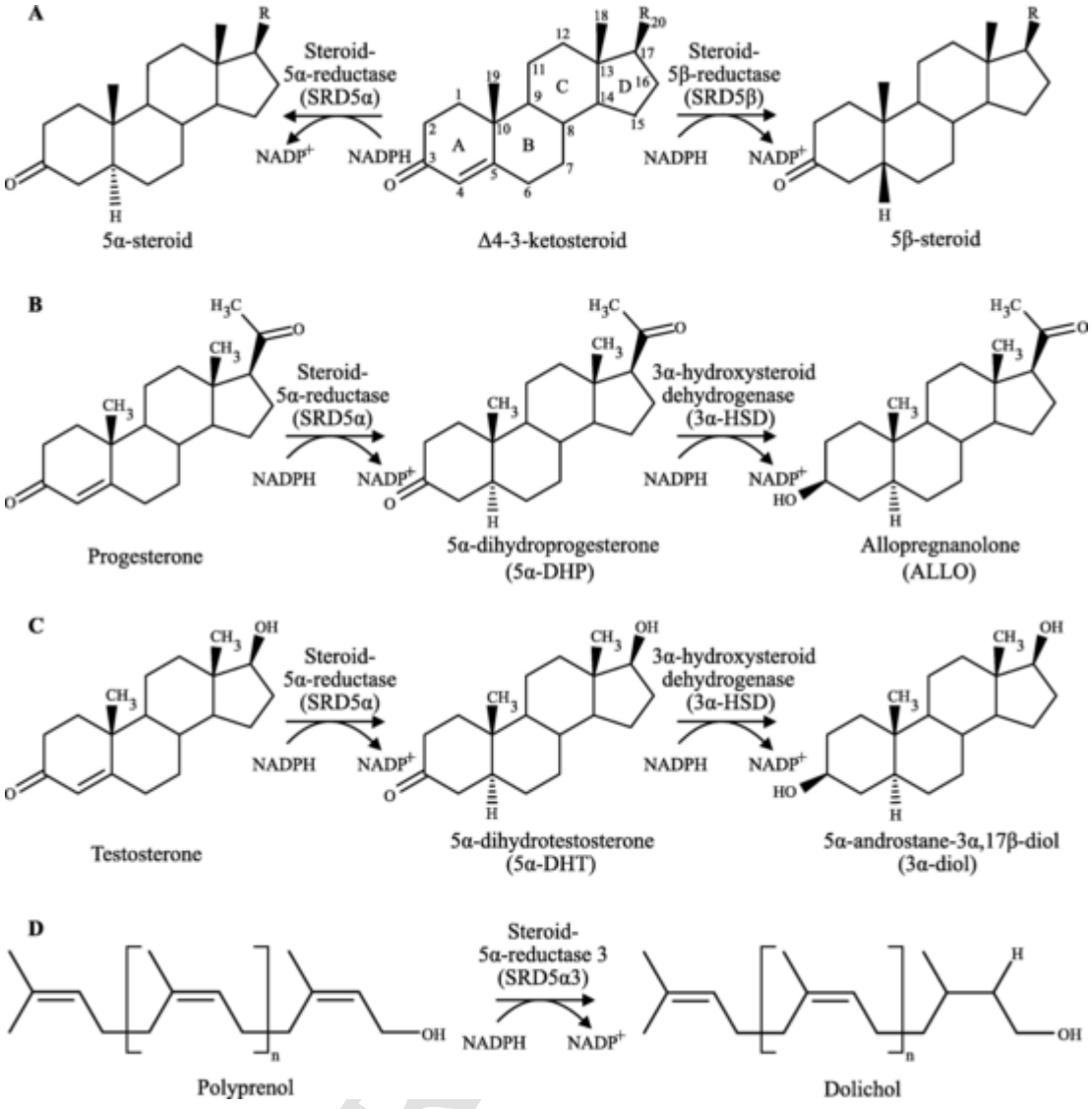

Fig. 1. Scheme of reactions performed by steroid-5α-reductase. (A) Scheme of the general reaction performed by SRD5α and SRD5β enzymes. The structure of the Δ4-3-ketosteroid is annotated with the nomenclature of steroids with the A, B, C and D ring and the numbering of each carbon atom. 5α-isomers are planar, while 5β-isomers have a 90° angle at the junction of the A and B ring. (B) Synthesis of neurosteroid allopregnanolone (ALLO) by reduction of progesterone into 5α-DHP by a SRD5α and into ALLO by 3α-HSD; (C) synthesis of neurosteroid 5α-androstane-3α,17β-diol (3α-diol) in the same way, testosterone is transformed into 5α-DHT, and finally in 3α-diol; (D) reduction of polyprenol into dolichol by SRD5α3.

al., 2013; SRD5α1/KO: Frye et al., 2004; Koonce and Frye, 2013), SRD5α2 is implicated mostly in the synthesis of the androgen 5α-DHT, and SRD5α3 is involved in N-glycosylation (Cantagrel et al., 2010). In order to differentiate between isoforms, studies rely on the difference in the optimum pH of their activity. SRD5α1 is known to have a broad spectrum pH optimum from pH 6–8.5, whereas SRD5α2′s optimum activity is more acidic around pH 5–5.5 (dog: Span et al., 1998; monkey: Levy et al., 1995; Ellsworth et al., 1998; hamster: Ramos et al., 2010; rat: Normington and Russell, 1992), and SRD5α3′s optimum pH is 6.5 (human: Titus et al., 2014).

2. History of 5α-reductase inhibitors (5ARIs)

The discovery of 5α-DHT's function in the development of secondary sexual male organs led to the development of finasteride (FIN), an irreversible inhibitor of SRD5α2. FIN was approved by the United States Food and Drug Administration in 1992 for the treatment of benign prostatic hyperplasia (BPH), and in 1997 for the treatment of androgenic alopecia, a loss of hair related to androgens. Since FIN's discovery, other 5α-reductase inhibitors (5ARIs) have been developed (reviewed by Aggarwal et al., 2010). Among all 5ARIs, FIN and dutasteride (DUT) are the most studied. FIN and DUT possess their own specificity for SRD5α isoforms. FIN is more specific to srd5α2 in primates (Levy et al., 1995; Yamana et al., 2010), since it induces the formation of an NADP-dihydroFIN adduct in the active site of SRD5α2 and inactivates the enzyme (Bull et al., 1996). However, FIN can also inhibit SRD5α1 in rats (Normington and Russell, 1992; Azzolina et al., 1997), and could also inhibit SRD5α3, as shown in human cells (Yamana et al., 2010). In contrast, DUT can inhibit both SRD5α1 and SRD5α2 in all mammals (Frye, 2006; Cabeza et al., 2016), and potentially SRD5α3 as well (Yamana et al., 2010; Titus et al., 2014).

Altogether, 5ARIs can inhibit more than one isoform of SRD5αs, which increases the possibility of developing unwanted side-effects when such compounds are administered. Men taking 5ARIs are known to develop erectile dysfunction and/or lose their libido (Gacci et al., 2014; Liu et al., 2016; Corona et al., 2017). Based on mouse studies, 5ARIs could increase anxiety and risk of seizure, which are linked to the loss of ALLO in the brain (Kokate et al., 1999; Frye et al., 2013). Moreover, the inhibition of SRD5α3 could lead to unforeseen side-effects, since humans lacking this isoform suffer from major morphological and physiological defects, such as heart malformation

Table 1
Localization of SRD5αs in the body and during development across species.

Species	Age and sex	Type of detection	Localization	Reference
Primate *Homo sapiens*	Fetus, newborn, adolescent, adult, ♂	WB, NB	SRD5α1: liver (except fetus), skin, balding scalp; adult: brain, chest skin; ND: adrenal gland, epididymis, kidney, prostate, testes, seminal vesicle, skeletal muscle SRD5α2: liver (except fetus), prostate (fetus not tested); adult: epididymis, prostate, seminal vesicle; ND: balding scalp, adrenal gland, kidney, skeletal muscle, chest skin, testes	Thigpen et al., 1993
	Fetus and adult, ♂	IH	SRD5α2: *fetus*: stroma of prostate, seminal vesicle, ejaculatory ducts, prostatic urethra, corpus cavernosum, spongiosum, pendulous urethra, scrotal skin, dorsal vein complex, external sphincter, Cowper's gland; ND: testes, epididymis, nerves of corpora cavernosum; *adult prostate*: stromal cells, basal/luminal epithelial cells of prostatic acini and prostatic fibroblast	Levine et al., 1996
	Adult, ♀♂	IH, NB, EA	SRD5α1and SRD5α2: *scalp of AGA patients*: ↑frontal than occipital follicles, SRD5α1 ↑ than SRD5α2 in ♀frontal follicles, both in outer root sheath and ↓dermal papilla	Sawaya and Price, 1997
	Adult, ♂	NB, RT-PCR with a gel	SRD5α1: testes, constant and ↓ throughout epididymis SRD5α2: ↑ in caput and distal caput of epididymis than other region, follow a gradient, ND in testes	Mahony et al., 1998
	Prostate of patients; preputial skin from 3 to 9 y.o, ♂	ISH	SRD5α1 and SRD5α2: *prostate* (adult): epithelial cells more than stroma; *preputial skin* (3–9 y.o): ↑ epidermis layers except stratum corneum, ↓ fibroblasts, secretory cells of sebaceous glands and excretory duct cells of sweat glands	Pelletier et al., 1998
	Adult, ♂	IH	No difference between normal scalp and AGA scalp SRD5α1: sebaceous gland, hair follicles, epidermis SRD5α2: hair follicles within the innermost layer of the outer root sheath, proximal region of hair follicles of ten extending into the inner root sheath, hair infundibular region, granular layer of epidermis, nerve sheath. Not dependent of follicle's phase	Bayne et al., 1999
	Fetus, neonate, 6 y.o, ♂	IH, RT-qPCR	SRD5α1: prostate epithelium more than stroma SRD5α2: prostate stroma more than epithelium Both ↑ at week 21 of gestation, ↓ until birth, ↑ at day 14 and ↓ until 4 months to 6 y.o SRD5α2: prostate stroma more than epithelium Both ↑ at week 21 of gestation, ↓ until birth, ↑ at day 14 and ↓ until 4 months to 6 y.o	Lunacek et al., 2007

Table 1 (*Continued*)

Species	Age and sex	Type of detection	Localization	Reference
Homo sapiens	Adult tissue, ♀♂	RT-qPCR	SRD5α3: brain (↑, also in fetus), liver, kidney, lung, heart, duodenum, retina, spleen, testes, placenta; *brain*: frontal, parietal and occipital cortex, cerebellum (↑), striatum, hippocampus (↑), thalamus, brain stem, spinal cord	Morava et al., 2010
	Adult tissue, ♀♂	RT-qPCR	SRD5α1: liver, kidney; ↑: brain (frontal cortex), skin (dermis, epidermis); ↓: lung, heart, muscle, pancreas, stomach, colon, small intestine, spleen, testes, prostate, ovaries, cervix, mammary gland SRD5α2: liver, kidney, muscle (↑), prostate (↑ in BPH patient); ↓: lung, heart, pancreas, stomach, colon, small intestine, testes, ovaries, cervix, spleen; ↓ to ND: brain, skin, mammary gland SRD5α3: liver, lung, muscle, colon; ↑: brain (frontal cortex), kidney, heart, stomach, small intestine, pancreas, spleen, skin (dermis, epidermis), testes, prostate, ovaries, cervix, mammary gland	Yamana et al., 2010
	Benign and malignant tissues, ♀♂	IH	SRD5α3: brain, thyroid, testes, breast, stomach, colon, esophagus, adrenal gland; ↑: liver, kidney, uterus, pancreas, skeletal muscle, skin; detection dependent on cancer type: bladder, lung, and ovaries; ND: spleen, endometrium, and tonsil	Godoy et al., 2011
Macaca fascicularis	Adult, ♂	RT-PCR with a.gel	SRD5α1: decreasing gradient in the epididymis, testes SRD5α2: constant throughout epididymis and ↑ than SRD5α1, ND in testes	Mahony et al., 1997
Macaca mulatta	Fetus and 2 y.o, ♂	EA	Fetus: SRD5α1: ↓: brain, liver, scalp and back skin, testes; SRD5α2: ↑: prostate, external genitalia, seminal vesicles; ↓: kidney, scrotal skin 2 y.o: SRD5α1: scalp skin; SRD5α2: prostate	Prahalada et al., 1997
Rats Sprague-Dawley	7w.o, ♀♂	NB	SRD5α1: brain, liver (↑), kidney, lung, muscle, stomach (↓), intestine (↑), colon, spleen (↓), adrenal gland, epididymis (↓ gradient); ↓: testes, vas deferens, seminal vesicle ovaries; ND:heart, prostate SRD5α2: adrenal gland (↓), colon (↓), intestine (↓), testes, epididymis (↑, small ↓ gradient throughout tissue), vas deferens, prostate, seminal vesicle; ND: brain, liver, kidney, lung, heart, muscle, stomach, spleen, ovaries	Normington and Russell, 1992

Table 1 (*Continued*)

Species	Age and sex	Type of detection	Localization	Reference
Sprague-Dawley	GD17 and 21, ♀♂	ISH, IH (only SRD5α1)	SRD5α1: ♂: epithelial cells of urogenital sinus, bladder, ureter (GD21), ventral and dorsal prostates (GD21), mesenchyme surrounding seminal vesicle anlage, not in epithelial cells of Wolffian and Mullerian ducts (GD17), ejaculatory ducts and vas deferens (GD21); ♀: epithelia of the urogenital sinus, bladder, rectum, Mullerian duct-derived portion (GD21) and vaginal plate (GD21) SRD5α2: GD17: ♂: mesenchyme of the urogenital sinus, urorectal septum (GD17), seminal vesicle; ND: mesenchyme surrounding bladder epithelium; ♀: mesenchyme urogenital sinus, rectum and symphis pubis (GD17) and mesenchyme of urethra and vagina (GD21)	Berman et al., 1995
	7–91 d.o, ♀♂	NB, IH	SRD5α1: liver (↑), kidney, testes (Leydig cells), ND in epididymis. In testes, ↓ from day 7–14, ↑ at day 21–28 and ↓ progressively with age SRD5α2: epididymis; ND: liver, testes	Viger and Robaire, 1995
	GD 14–18, PN 2–28, adulthood, ♀♂	RT-PCR with SB	SRD5α1: prostate, constant in brain for all age tested SRD5α2: prostate, not expressed in the brain at GD14 and 16, ↑ in between GD18-PN2 and ND in adulthood	Poletti et al., 1998
	10–160 d.o, ♂	RT-qPCR, EA	SRD5α1 and SRD5α2: in testes, ↑ from day 20 to 40 (puberty) and ↓ with age. SRD5α1 always ↑ than SRD5α2	Killian et al., 2003
	Adult, ♂	RT-PCR + SB	SRD5α1: constant in brain, spinal cord and prostate SRD5α2: ↑: spinal cord, prostate; ↓: brain (motor neurones of the anterior horn and perinuclear region)	Pozzi et al., 2003
	Adult, ♂	IH	SRD5α2: brain: olfactory bulb, cortical area, basal ganglia, septum, amygdala, hippocampus, habenula, thalamus, hypothalamus, midbrain (↓), pons (↓), rhombencephalon, cerebellum (high only in Purkinje cells). Type of neurons: Purkinje cells, pyramidal and GABAergic neurons	Castelli et al., 2013
Wistar	Adult, ♀♂	WB, EA, IH	SRD5α1: olfactory bulb (astrocytes, oligodendrocytes and olfactory ensheathing cells), liver	Kiyokage et al., 2005
	P0- 6 w.o, ♀♂	WB, EA, IH	SRD5α1: cerebellum (Bergmann glia, astrocytes, oligodendrocytes) SRD5α1: liver (↑), skeletal muscle, adipose tissue SRD5α2: liver, adipose tissue	Kiyokage et al., 2014
Mice C57BL/6J /129Sv	Adult, ♀♂	NB	SRD5α1: liver (↑), kidney, skin, epididymis, testes, vas deferens, ovaries, uterus; ↓: brain, adrenal gland, testes, vas deferens	Mahendroo et al., 1996

Table 1 (*Continued*)

Species	Age and sex	Type of detection	Localization	Reference
			SRD5α2: adrenal gland (↓ in ♀), kidney, prostate, epididymis, vas deferens, ND: brain, liver, skin, testes	
Heterozygous SRD5α3 mutant with LacZ gene	GD 10.5–15.5 and PN 5	Whole-mount β-gal coloration	SRD5α3: GD10.5–12.5: eye, branchial archs, limbs, umbilical cord, yolk sac, heart and neural tube; GD15.5: same but lower in gut and choroid plexus; PN5: ↓ in hippocampus	Cantagrel et al., 2010
Heterozygous SRD5α3 mutant with LacZ gene	Adult, ♀♂	RT-qPCR	SRD5α1: bone, heart; ↑: liver, epididymis, prostate SRD5α2: liver; ↑: epididymis, prostate; ↓: bones, heart SRD5α3: ↑: liver, bones, heart, epididymis, prostate	Windahl et al., 2011
Swiss-Webster	Adult, ♂	IH	SRD5α1: brain: cortex, hippocampus, olfactory bulb, striatum, thalamus, amygdala and cerebellum	Agis-Balboa et al., 2006
Hamster (*Mesocricetus auratus)*	12 w.o, ♀♂	RT-qPCR	SRD5α3: adrenal gland, epididymis, liver, pancreas, seminal vesicles, ↑: brain (cerebellum), Harderian gland, testes; ↓: lung, ovaries, uterus, spleen	Chávez et al., 2015
Muskrat (*Ondatra zibethicus*)	Adult, ♂	WB, RT-qPCR, IH	SRD5α2: testes, scented gland	Han et al., 2017
Beagle dog	Adult, ♂	RT-PCR with SB, EA	SRD5α1: *mRNA*: cardiac muscle, adrenal gland, prostate, brain (cerebrum and cerebellum), liver, lung, testes (↑), pectoral muscle, ND: bladder; *enzyme*: ↑: kidney, epididymis, prostate; ↓: brain (cerebrum and cerebellum), adrenal gland, liver, testes; ND: cardiac muscle, lung, spleen, bladder wall, pectoral muscle SRD5α2: *mRNA*: liver (↑); ↓: brain (cerebrum and cerebellum), bladder, testes, pectoral muscle; ND: cardiac muscle, adrenal gland, prostate; *enzyme*: ↑: kidney, epididymis, prostate; ↓: brain (cerebrum and cerebellum), adrenal gland, liver; ND: cardiac muscle, lung, spleen, bladder wall, pectoral muscle, testes	Span et al., 2000
	Adult, ♀♂	RT-qPCR	SRD5α1: prostate (↓), skin (↓, except in ♀ thorax skin in which ↑) SRD5α2: prostate (↓), ND in skin SRD5α3: prostate (↓), skin (↓, except in ♀ thigh and thorax skin in which ↑)	Bernardi de Souza et al., 2015
Bird *Coturnix cortunix japonica*	Adult, ♀♂	EA	SRD5α: brain: nucleus taenia, hyperstriatum (↓), septum, anterior hypothalamusipreoptic area, posterior hypothalamus, midbrain containing nucleus intercollicularis (↓), cerebellum (↓) and pituitary	Schlinger and Callard, 1987

Table 1 (*Continued*)

Species	Age and sex	Type of detection	Localization	Reference
	Adult, ♂	EA	SRD5α: nucleus preopticus dorsolateralis, nucleus preopticus medialis, nucleus anterior hypothalamic, area lateralis hypothalamic, nucleus paraventricularis, nucleus ventromedialis hypothalamic, bed nucleus pallial commissure, nucleus septalis medialis, nucleus septalis lateralis, archistriatum pars ventralis, nucleus rotundus	Schumacher and Balthazart, 1987
Phalaropus tricolor	Adult, ♀♂	EA	SRD5α: brain (anterior hypothalamus/preoptic area, posterior hypothalamus, septum, archistriatum, hyperstriatum, pituitary), scapular skin (↑in ♀)	Schlinger et al., 1989
Parus major	Juvenile and adult, ♂	EA	SRD5α: brain: anterior and posterior hypothalamus, cerebellum	Silverin and Deviche, 1991
Melospiza melodia morphna	Adult, ♂	EA	SRD5α: brain: hippocampus (↑), ventromedial telencephalon, caudomedial neostriatum and diencephalon (DIEN)	Soma et al., 2003
Manacus vitellinus	Adult, ♀♂	RT-qPCR	SRD5α1: spinal cord (cervical, thoracic and lumbar; always ↑ in ♂), muscle (*supracoracoideus* (↓ in ♀), *scapulohumeralis caudalis*, *pectoralis*) SRD5α2: spinal cord (cervical, thoracic and lumbar), muscle (*supracoracoideus*, *scapulohumeralis caudalis* (↑ in ♀), *pectoralis*)	Fuxjager et al., 2016
Taenoygia guttata	Adult, ♀♂	RT-qPCR	SRD5α1: spinal cord (cervical, thoracic and lumbar), muscle (*supracoracoideus*, *scapulohumeralis caudalis* (↓ in ♀), *pectoralis*) SRD5α2: spinal cord (cervical, thoracic and lumbar), muscle (*supracoracoideus*, *scapulohumeralis caudalis* (↑), *pectoralis*)	Fuxjager et al., 2016
Lizard *Anolis carolinensis*	PN0-PN50	ISH	SRD5α1 and SRD5α2: brain: anterior dorsal ventricule ridge (↑), dorsal cortex (↑), nucleus accumbens, bed nucleus of the stria terminalis (SRD5α1: ND; SRD5α2: ↓), preoptic area, ventromedial amygdala, spetum (↓), ventromedial hypothalamus, torus semicircularis, oculomotor nucleus, trigeminal motor regions (↑), trochlear nucleus, nucleus ambiguus, spinal accessory and hypoglossal nuclei	Cohen and Wade, 2012
Frog *Xenopus laevis*	NF12-66	RT-PCR with a.gel	NF59: SRD5α1: brain, liver, kidney, heart, gonads, spleen; SRD5α2: gonads (↑ in ♂), brain (↓) and kidney, ND in heart, liver, spleen NF12-48: SRD5α1 ↑ at NF12, ↓ with development; SRD5α2 little ↑ at NF39-44 and ↓ NF48-66: SRD5α1 ↓ in kidney from NF 48–54 and stay stable; ↑ a little in brain during development; SRD5α2 ↓ from NF 48–54 and ↑ in ♂ kidney after differentiation and in the brain, ↓ from NF48-54	Urbatzka et al., 2007

Table 1 (*Continued*)

Species	Age and sex	Type of detection	Localization	Reference
Rana esculenta	Brain, stage IV-XXV	IH	SRD5α1: Stage IV: anterior olfactory nucleus, ↓: glomerular layer of olfactory bulb, nucleus of Broca's diagonal band, anterior preoptic area. Stages V–IX: similar as before and dorsal pineal gland, medial longitudinal fascicle Stages X–XII: similar as before and telencephalon (dorsal pallium), hypothalamus (preoptic nucleus), mesencephalon (posterocentral nucleus), cerebellum (Purkinje cells) and pituitary (distal lobe) Stages XIII–XVIII: similar as before and telencephalon (septum, ventral striatum medial and lateral amygdala), diencephalon (anterior preoptic area, ventrolateral area of the thalamus, ventral and dorsal infundibular nuclei), mesencephalon (anteroventral nucleus, anterodorsal nucleus, semicircular torus, posterolateral nucleus, optic tectum, interpeduncular nucleus) Stages XIX–XXV: similar as previous stage Stages V–IX: similar as before and dorsal pineal gland, medial longitudinal fascicle Stages X–XII: similar as before and telencephalon (dorsal pallium), hypothalamus (preoptic nucleus), mesencephalon (posterocentral nucleus), cerebellum (Purkinje cells) and pituitary (distal lobe) Stages XIII–XVIII: similar as before and telencephalon (septum, ventral striatum medial and lateral amygdala), diencephalon (anterior preoptic area, ventrolateral area of the thalamus, ventral and dorsal infundibular nuclei), mesencephalon (anteroventral nucleus, anterodorsal nucleus, semicircular torus, posterolateral nucleus, optic tectum, interpeduncular nucleus) Stages XIX–XXV: similar as previous stage	Bruzzone et al., 2010
Rana rugosa	Stage 25, I, III and V, ♀♂	RT-qPCR	SRD5α1: present in both sex at all stages in similar small quantities	Maruo et al., 2008
Silurana tropicalis	Adult, ♀♂	RT-qPCR	SRD5α1: ↑: liver; ↓: brain and gonads SRD5α2: ↑: testes; ↓: ovaries; ND: brain and liver SRD5α3: ↑: liver and testes; ↓: brain and ovaries	Bissegger and Langlois, 2016b
	NF2-46	Whole mount ISH	SRD5α1: brain (telencephalon, midbrain), spinal cord, neural plate, notochord, liver (↑), hepatic diverticulum, pronephric kidney, heart, stomach, hindgut, intestine, otic vesicle, pharyngeal pouch, yolky endoderm	Bissegger and Langlois, 2016a

Table 1 (*Continued*)

Species	Age and sex	Type of detection	Localization	Reference
			SRD5α2: brain (↓), spinal cord, neural plate, liver, cloaca, heart, stomach, intestine, otic vesicle, pharyngeal pouch, yolky endoderm SRD5α3: brain (midbrain, forebrain), spinal cord, neural tube, liver, heart, heart anlage, visceral pouch, stomach, intestine, otic vesicle, pharyngeal pouch, gills, yolky endoderm	
Fish *Pimephales promelas*	1–14 dpf and adult, ♀♂	RT-qPCR	SRD5α1: 1dpf: high ; 3–14 dpf: low; adult: brain, liver, ovary and testis SRD5α2: relatively low from 1 to 14 dpf in comparison to other SRD5α, ↑ a little at 6 dpf; adult: brain (higher than other isoform), liver (higher in ♂ and higher than other isoform), ovary and testis (higher than in ovary) SRD5α3: 1dpf: high; 3–14 dpf: low; adult: brain, liver, ovary (higher than in testis) and testis	Martyniuk et al., 2013
Protopterus annectens	Adult, ♂	IH	SRD5α1: Brain: telencephalon (intercalate nucleus, subpallium, medial, dorsal, and lateral pallium), diencephalon (periventricular preoptic nucleus, ventral and dorsal hypothalamic nuclei, dorsal and ventral thalamus), mesencephalon (caudal part of the tectum, periaqueductal gray), rhombencephalon (visceral area), pituitary (pars distalis). Label ependymocytes and neurons; testes: Leydig cells	Mathieu et al., 2001
Carassius auratus	Adult, ♀♂	EA	SRD5α: ↓ gonads and muscle; brain: pituitary, telencephalon, hypothalamus and preoptic area, midbrain, cerebellum, spinal cord	Pasmanik and Callard, 1985
Opsanus tau	Adult, ♀♂	EA	SRD5α: ↓ to undetectable in every part of the brain, gonads and muscle	Pasmanik and Callard, 1985

Abbreviations: AGA: androgenic alopecia; a.gel: agarose gel; d.o: days old; dpf: day post fertilization; EA: Enzymatic assay; GD: gestational days; IH: Immuno-histochemistry; ISH: *in situ* hybridization; NB: Northern blot; ND: not detected; NF: Nieuwkoop-Faber stages; PN: postnatal days; SB: Southern blot; w.o: week old; WB: Western blot; y.o: year old.

and mental retardation (Cantagrel et al., 2010). These examples show a glimpse of the importance of SRD5αs. In the last decades, significant progress has been made in understanding SRD5αs' roles, nevertheless there are still numerous research questions related to their functions, especially in non-mammalian species. To identify the many functions of SRD5αs across vertebrates, this review compiles literature on SRD5α deficiency induced by both mutation and inhibition with 5ARIs. The review highlights the molecular and physiological mechanisms by which SRD5αs are involved in male development via 5α-DHT, the role of ALLO in behaviour, as well as lesser known functions of SRD5αs such as their role in pregnancy and childbirth, glucocorticoid clearance and N-glycosylation. The functions of SRD5αs described in the review are summarised in Figure 2. The review also explores the known mechanism of regulation of *SRD5αs* by transcription factor and epigenetic regulation and highlights which pathways should be explored further to improve our knowledge of SRD5αs' regulation across tissues and species.

3. Consequences of a lack of 5α-DHT

3.1. Impacts on male secondary sexual organs

T is converted into 5α-DHT directly in the targeted tissue, which is the reason why SRD5α2 is expressed throughout the body, but mainly in male secondary sexual organs such as the prostate, epididymis and penis (Table 1). A lack of SRD5α2 activity decreases 5α-DHT levels in those tissues, which decreases overall 5α-DHT levels in the serum of vertebrates (human: Park and Choi, 2014; monkey: Rhodes et al., 1994; rat: George et al., 1989; George, 1997; Prahalada et al., 1998; Pinsky et al., 2011; Garcia et al., 2012; Zhang et al., 2012; Enatsu et al., 2017; SRD5α2/KO mice: Mahendroo et al., 2001; fish: García-García et al., 2017). As 5α-DHT promotes the development of secondary sexual organs, a decrease in its synthesis can lead to adverse effects in androgen-dependent organs as described in the following sections.

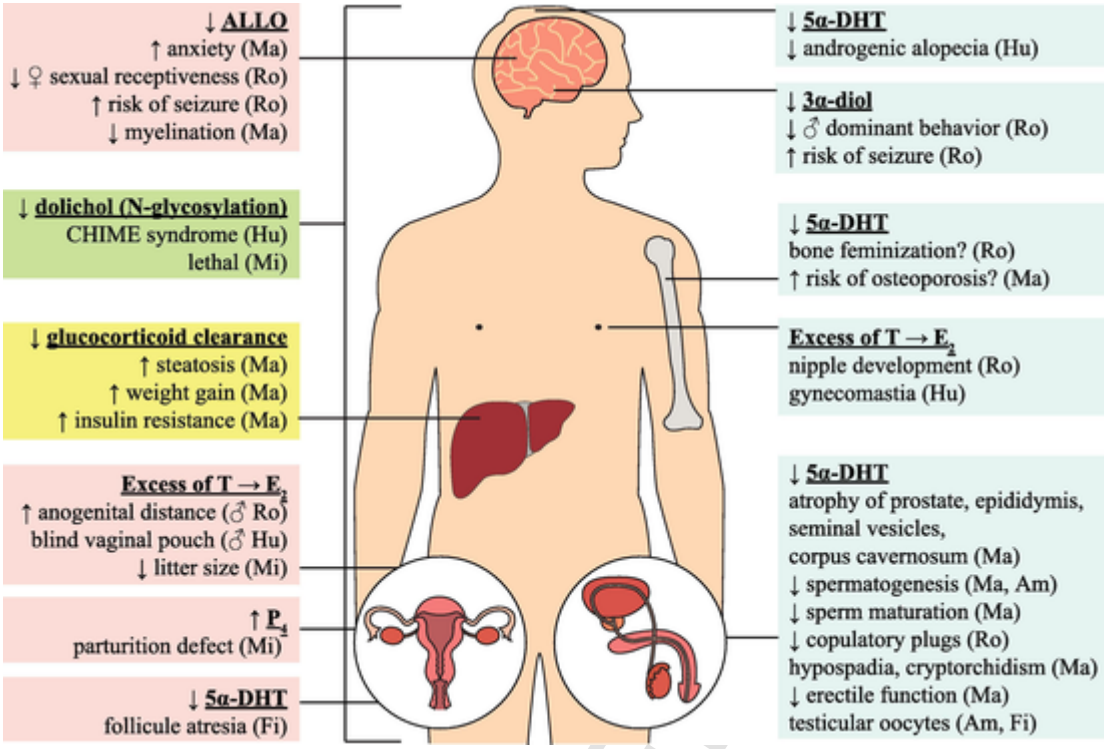

Fig. 2. Comparative physiological consequences of a lack of SRD5α in vertebrates (amphibians: Am; fish: Fi; humans: Hu; mammals: Ma; mice: Mi; rodents: Ro). Lack of SRD5α can decrease 5α-DHT and adversely affect secondary sexual tissues (penis, scrotum, prostate, epididymis, and seminal vesicles), hair growth and bone structure, as well as cause female biased sex ratio in amphibians. Simultaneously, the excess of T can be converted to E_2, which can increase breast development, anogenital distance, vaginal development and decrease litter size. The absence of SRD5α activity can also decrease the degradation of P_4 involved in mice parturition, as well as slowing glucocorticoid clearance which increases steatosis, weight gain and insulin resistance. SRD5αs are also implicated in ALLO synthesis in the brain. A decrease in ALLO increases anxiety, risk of seizure, and decreases myelination. Also, lower levels of 3α-diol in the brain can lead to a decrease in aggressiveness and dominance. Finally, SRD5α3 deficiency leads to a decrease in dolichol, which impacts N-glycosylation and leads to a CHIME syndrome in human and to lethality in mice. Of note, the human schematic was only used as an example. Abbreviations: 3α-diol: 5α-androstane-3α,17β-diol; 5α-DHT: 5α-dihydrotestosterone; ALLO: allopregnanolone; CHIME syndrome: ocular colobomas, heart defects, ichthyosiform dermatosis, mental retardation and ear defects or epilepsy; E_2: estrogen; P_4: progesterone; T: testosterone.

3.1.1. Atrophy of androgen-dependent organs

The most well-documented consequence of a decrease in 5α-DHT in mammalian species is the reduction of the prostate weight (human: Kang et al., 2014; Park and Choi, 2014; Mendonca et al., 2016; dog: Juniewicz et al., 1993; Laroque et al., 1994; rats: George et al., 1989; Imperato-McGinley et al., 1992; Clark et al., 1993; Shao et al., 1993; Prahalada et al., 1998; Cayatte et al., 2006; Zhang et al., 2012; Giatti et al., 2016; Enatsu et al., 2017; mice: Mahendroo et al., 2001; wallaby: Ryhorchuk et al., 1997). The absence of 5α-DHT can also lead to weight loss of androgen-dependent organs, such as the epididymis (rat: George et al., 1989; Cayatte et al., 2006; Garcia et al., 2012), seminal vesicles (rat: George et al., 1989; Imperato-McGinley et al., 1992; Cayatte et al., 2006; Enatsu et al., 2017), corpus cavernosum (rat: Zhang et al., 2012; Enatsu et al., 2017), and Cowper's gland (rat: Cayatte et al., 2006). However, in some cases this weight reduction is not seen (e.g., epididymis: men: Kang et al., 2014; Mendonca et al., 2016; dog: Juniewicz et al., 1993; Laroque et al., 1994; rat: Imperato-McGinley et al., 1992; seminal vesicle: men: Kang et al., 2014; Mendonca et al., 2016; monkey: Prahalada et al., 1997). Also, the vas deferens weight does not seem to be affected by a lack of 5α-DHT (men: Kang et al., 2014; Mendonca et al., 2016; rat: Imperato-McGinley et al., 1992). Some of the prostate studies have suggested that this decrease in androgen-dependent organ weight is the result of the tissue atrophy (dog: Juniewicz et al., 1993; Laroque et al., 1994; rat: Cayatte et al., 2006; Enatsu et al., 2017), which is showed by a significant decrease of cell proliferation (rat: Cayatte et al., 2006), the presence of fibrosis (rat: Enatsu et al., 2017), the increase in apoptotic prostatic cells in ejaculate (dog: Sirinarumitr et al., 2002), and the alteration of tissue morphology (rat: Enatsu et al., 2017; gerbil: Corradi et al., 2004). Similar signs of fibrosis and atrophy can be observed in the corpus cavernosum (rat: Pinsky et al., 2011; Enatsu et al., 2017). On the molecular level, the absence of cell proliferation is related to a lesser activation of AR receptors. In the epididymis of FIN-treated rats, ARs are localized in the cytoplasm, in contrast to controls in which ARs are mainly located in the nucleus (Trybek et al., 2005). Hence, ARs are not able to translocate to the nucleus due to a lack of 5α-DHT, which prevents activation of transcription needed for cell proliferation in androgen-dependent organs and explains the observed weight loss.

3.1.2. Developmental defects

A lack of 5α-DHT can also lead to a defect in the male genital tubercle development. The genital tubercle has the potential to develop either into a penis and scrotum in males, or a clitoris and vagina in females (Yamada et al., 2003; Blaschko et al., 2012). In males, the differentiation of the structure is regulated by androgens. The loss of 5α-DHT production consequently leads to hypospadia, a congenital disorder causing the urethra to be mislocated on the underside of the penis (human: Kang et al., 2014; Mendonca et al., 2016; monkey: Prahalada et al., 1997; rats: Clark et al., 1990; Imperato-McGinley et al., 1992; Clark et al., 1993; rabbit: Kurzrock et al., 2000). The hypospadia condition is the result of a failure during the fusion process between the urethral groove and the genital tubercle, which, normally in the presence of 5α-DHT, would form the penile urethra (Yamada et al., 2003; Blaschko et al., 2012). In addition to hypospadia, SRD5α2-deficient men can also exhibit a bifid scrotum (

Kang et al., 2014), whereas monkeys treated with FIN have preputial adhesions, prominent midline raphe, and an underdeveloped scrotum (Prahalada et al., 1997). Moreover, cleft prepuces have been observed in rats (Clark et al., 1990; Imperato-McGinley et al., 1992; Clark et al., 1993). The most sensitive period for FIN to induce such effects in rats is from the gestational days 16–17 (Clark et al., 1993), which correlates with the development of the genital tubercle, occurring during weeks 8 to 12 of pregnancy in humans, and gestational days 11–16 in mice (Blaschko et al., 2012). During these stages of development, the fate of the male genital tubercle appears to depend on the expression of *SRD5α2* in mesenchymal cells of the tubercle. Those cells seem to play an instructive role for the epithelial cells as suggested by Berman et al. (1995). This correlates with the expression pattern of *SRD5α1* and *SRD5α2* in the urogenital tract where *SRD5α1* is confined in epithelial cells and *SRD5α2* to the mesenchymal cells (Table 1).

Additionally, the lack of SRD5α2 activity increases T levels (human: Park and Choi, 2014; monkey: Rhodes et al., 1994; rat: George et al., 1989; George, 1997; Prahalada et al., 1998; Ribeiro and Pereira, 2005; fish: García-García et al., 2017). During fetal development T can be converted in E2 by aromatase and promote the differentiation of the urogenital sinus in females (Blaschko et al., 2012). Indeed, SRD5a2 deficiency leads to the development of a blind shallow vaginal pouch in men (Kang et al., 2014) and to a decrease of the anogenital distance (rat: Clark et al., 1990; Clark et al., 1993; rabbit: Kurzrock et al., 2000); however, this condition is not always observed (monkey: Prahalada et al., 1997; rats: Ribeiro and Pereira, 2005). Moreover, the produced E_2 induces nipple development in rats (Clark et al., 1990; Imperato-McGinley et al., 1992; Clark et al., 1993) and leads, on rare occasion, to gynecomastia at puberty in SRD5α2-deficient men (Mendonca et al., 2016).

Another developmental defect due to a lack of 5α-DHT is cryptorchidism, in which testes are undescended (SRD5α2-deficient men: Kang et al., 2014; Mendonca et al., 2016; monkey: Prahalada et al., 1997). However, cryptorchidism is rarely observed in rats (Clark et al., 1990; Imperato-McGinley et al., 1992). The difference between primates (including humans) and rodents can be explained by a difference of periods when the testicular descent takes place. The testicular descent is split into two phases: the transabdominal phase and the inguinoscrotal phase. The transabdominal phase consists of testes migration through the iguinal region, which is an insulin-like hormone 3 (INSL3)-dependent process. This phase usually takes place during week 10 to 15 of gestation in humans, while in rodents it happens around gestational days 13–17. In the inguinoscrotal phase, testes descend through the inguinal canal to the scrotum using an androgen-dependent mechanism, which occurs from gestational week 25 to 35 in humans and during postnatal week 3–4 in rodents (Hutson et al., 2013). Since the androgen-dependent phase occurs after birth in rodents, inhibition of 5α-DHT production during gestation does not affect as strongly the testicular descent in rats in comparison to primates.

3.1.3. Disruption of erectile function

Men treated for BPH have up to 156% increased risk of developing erectile dysfunction (Gacci et al., 2014; Liu et al., 2016; Corona et al., 2017), while no significant side effects on erectile dysfunction were found in cohorts of patients treated for androgenic alopecia (Liu et al., 2016). However, the assessment of 5ARIs' impact on erectile dysfunction in men is currently limited by a lack of method standardisation as highlighted by three recent meta-analyses on the subject (Gacci et al., 2014; Liu et al., 2016; Corona et al., 2017). In 5ARI-treated rats, erectile function is also decreased (Pinsky et al., 2011). This loss of function can be in part due to tissue atrophy as discussed earlier (rat: Pinsky et al., 2011; Enatsu et al., 2017), as well as to a decrease in neuronal nitric oxide synthase (NOS), essential for penile erection (Pinsky et al., 2011). Indeed, lower neuronal NOS activity impacts levels of nitric oxide, a key mediator of erectile function in cavernosal nerves. In an effort to counteract the loss of neuronal NOS, the body increases other members of the NOS family, such as the inducible NOS, to try to counter fibrosis and oxidative stress in the penile tissue. However, the production of inducible NOS does not seem to be enough in rats to prevent a loss of function (Pinsky et al., 2011). It is possible the same phenomenon happens in other mammals, suggesting a constant exposure to 5ARIs could lead to permanent damage to the penile tissue.

3.1.4. Effects on spermatogenesis and the structure of seminiferous tubules

A decrease in 5α-DHT has no effects on testis weight (dog: Juniewicz et al., 1993; Laroque et al., 1994; rat: Rhoden et al., 2002; SRD5α2/KO mice: Mahendroo et al., 2001; wallaby: Ryhorchuk et al., 1997), nor on the presence of spermatogonia (SRD5α2-deficient men: Kang et al., 2014; Mendonca et al., 2016; wallaby: Ryhorchuk et al., 1997; amphibian: Urbatzka et al., 2009; fish: Margiotta-Casaluci et al., 2013). However, spermatogenesis progression was impaired as confirmed by a decrease in the production of spermatocytes and spermatids (SRD5α2-deficient men: Kang et al., 2014, amphibian: Urbatzka et al., 2009). Additionally, hypotrophy of seminiferous tubules can occur (hamster: Vidigal et al., 2008; wallaby: Ryhorchuk et al., 1997). In FIN-treated amphibians (*Xenopus laevis*), testes are immature and exhibit empty spermatocyst cavities (Urbatzka et al., 2009). This suggests that a decrease in 5α-DHT can affect spermatogenesis, as well as the structure of seminiferous tubules/spermatocysts. These effects indicate that Sertoli cells are mainly affected by the lack of 5α-DHT, since they are involved in spermatogenesis by supporting germ cells' development, as well as playing an important role in the structure of the seminiferous tubules and the maintenance of the blood-testis barrier (Wang et al., 2009; Huhtaniemi, 2018). The impact on Sertoli cells could be linked to the high intratesticular T concentration found in the testes, which is secreted by Leydig cells and known to promote spermatogenesis (Wang et al., 2009; Huhtaniemi, 2018). This high intratesticular T concentration is probably converted locally into 5α-DHT in the Sertoli cells which express *SRD5α2* (Table 1). Hence, 5α-DHT is implicated in spermatogenesis and the maintenance of the seminiferous tubules in Sertoli cells. The only exception to this rule being 5ARIs-treated fish in which spermatogenesis is unaltered or even increased because levels of T and 11KT, the most potent androgen in fish, are increased (Margiotta-Casaluci et al., 2013; García-García et al., 2017).

3.1.5. Effects on sperm maturation and fertilization

After spermiation in the testes, the spermatozoids are matured in the epididymis to acquire motility and increase their fertilization potential. This process is known to be androgen-dependent (Cornwall, 2008; Sullivan and Mieusset, 2016). Indeed, *SRD5α2* (Table 1), *AR* and the androgen binding protein, which transports T to the epididymis, are expressed throughout the epididymis (Robaire and Hamzeh, 2011). Hence, a lack of 5α-DHT leads to the atrophy of the epididymis, as discussed previously. In FIN-treated rats, daily sperm production was not altered (George et al., 1989; Rhoden et al., 2002; Ribeiro and Pereira, 2005; Garcia et al., 2012), but their sperm motility was impaired by the atrophy (Ribeiro and Pereira, 2005; Garcia et al., 2012). Additionally, the motility was not recovered after FIN-withdrawal (Garcia et al., 2012), which suggests a long term impact on fertility. Similarly, SRD5α2-deficient men exhibited decreased sperm motility (Kang et al., 2014; Mendonca et al., 2016), which is rarely observed in men treated with 5ARIs (Amory et al., 2007). Overall, 5α-DHT plays a crucial role in the epididymal structure by maintaining cell proliferation, epithelial cell height and lumen diameter (Robaire and Hamzeh, 2011). To preserve the structure of the epididymis, 5α-DHT regulates gene expression through ge-

nomic response via AR and rapid non-genomic response via the extracellular receptor kinase pathway (Hamzeh and Robaire, 2011). Among the genes regulated by 5α-DHT, the insulin-like growth factor-I and the epidermal growth factor appear to play a main part in the promotion of cell proliferation (Hamzeh and Robaire, 2010).

To ensure fertilization success, the ejaculate of some species (notably rodents) coagulates into copulatory plugs in the vagina of females. As well as indicating successful coitus, copulatory plugs gradually release spermatozoids, promote sperm transport, and can prevent other males from mating the same female (Schneider et al., 2016). In rats, FIN treatment decreased the capacity to form copulatory plugs by 50%, which impacted fertilisation rates (Cukierski et al., 1991). The observed decrease originates from the atrophy of the prostate and the seminal vesicle, which produce the proteins responsible for the formation of copulatory plugs (Schneider et al., 2016).

3.1.6. Effects on sex determination in non-mammalian vertebrates

A lack of 5α-DHT can affect testes differentiation in genetic males of non-mammalian species, while mammalian gonads still differentiate into testes. In male common toad (*Bufo bufo*), treatment with β4-androstene-3-one-17β-carboxylic acid (17βC) (another 5ARI) led to larger oocytes in Bidder's organs (a rudimentary ovary found in the gonad of both sexes), and to sex reversal of the actual testes (Petrini and Zaccanti, 1998). In the western clawed frog (*Silurana tropicalis*), chronic exposure to FIN induced a female biased sex ratio; with 27% males, 53% females, and 20% exhibiting testicular oocytes, an intersex condition (Duarte-Guterman et al., 2009; Langlois et al., 2011). In male medaka (*Oryzias latipes*), testicular degeneration and presence of testicular oocytes were observed when exposed to FIN from the fertilized egg stage to sexual maturity (Lee et al., 2015). These results suggest 5α-DHT can affect the sex determination of gonads. This contrasts with mammals in which sex determination is independent of hormones, except for marsupials (Hayes, 1998; Nakamura, 2013; Trukhina et al., 2013; Capel, 2017).

3.1.7. Impaired bone development and retention

In mice, SRD5α1/KO males have showed reduced bone mass and forelimb muscle grip strength. The observed partial feminization of the skeleton suggests 5α-DHT is needed for normal development of bone and muscle in male mice (Windahl et al., 2011). In contrast, SRD5α2-deficient men (Mendonca et al., 2016) and FIN-treated men (Amory et al., 2008; Macukat et al., 2014) do not exhibit differences in bone density. DUT could even have osteoprotective effects based on increased bone density observed in a patient cohort (Macukat et al., 2014). The osteoprotective effect is probably time dependent, since no effects on bone density were observed after 52 weeks of treatment (Amory et al., 2008), but an increase in density was observed after 24 to 48 months (Macukat et al., 2014). In contrast, FIN-treated patients have an increased risk to develop osteoporosis (Lin et al., 2015). It has also been suggested that the lack of SRD5α activity would impact the levels of glucocorticoids, which are also involved in bone maturation (Warriner and Saag, 2013). However, 5α-DHT has more potential to be linked to the role of SRD5αs in bone development since *in vitro,* 5α-DHT increases the proliferation of epiphyseal chondrocytes and osteoblasts, both implicated in longitudinal bone growth (Gori et al., 1999; Krohn et al., 2003; Raz et al., 2005). The observed increase in cell proliferation is mediated by the 5α-DHT-induced synthesis of insulin-like growth factor-I (Gori et al., 1999; Krohn et al., 2003).

3.1.8. Effects on the abundance and distribution of body and scalp hair

SRD5α2-deficient men exhibit less body hair growth than other men and their hair distribution follows a female pattern (Randall, 2008). In contrast, women overproducing 5α-DHT in their skin suffer from hirsutism, a condition in which body hair overgrows in regions associated with a male pattern. Hirsutism can be treated with FIN (van Zuuren and Fedorowicz, 2016; Barrionuevo et al., 2018), indicating 5α-DHT has a role in body hair growth. At puberty, 5α-DHT stimulates hair growth of small and colorless hair, called vellus follicles, which will grow into thick, long, and pigmented hair known as terminal follicles as can be found on the chin, chest, pubis, arms, legs, and back of post-pubescent men (Randall, 2008). Paradoxically, 5α-DHT has a deleterious effect on scalp hair growth. In the scalp, the presence of 5α-DHT induces hair miniaturization by converting terminal hairs into vellus hairs (Randall, 2008; Urysiak-Czubatka et al., 2014). In men, 5ARIs can reduce androgenic alopecia (Gupta and Charrette, 2013; Adil and Godwin, 2017), while no baldness pattern is observed in SRD5α2-deficient men (Kang et al., 2014; Mendonca et al., 2016). Also, in Stumptail macaque (*Macaca arctoide*), a model for androgenic alopecia, FIN treatment slightly improved hair growth by increasing the number of scalp hair follicles and their average length (Rhodes et al., 1994). However, FIN is not an efficient therapy for women suffering from androgenic alopecia (Adil and Godwin, 2017). The reasons leading to the sex difference in treatment efficacy remain unclear. However, *SRD5α1* is expressed more than *SRD5α2* in the scalp of women suffering from androgenic alopecia (Sawaya and Price, 1997), which suggests that DUT treatment would be more successful. It would also be the case in men, since a study showed *SRD5α2* was no longer expressed in the balding scalp, while *SRD5α1* was still expressed (Thigpen et al., 1993).

3.2. Impacts on female reproductive system

3.2.1. Effects in the uterus during gestation

A novel SRD5α2 mutation increased the risk of miscarriage in women (Pérez-Nevot et al., 2017). However, the molecular mechanism by which the mutation leads to miscarriage is still unclear. In female mice, 67% of SRD5α1/KO suffered from a defect in parturition, which could lead to complications, such as vaginal bleeding, resorption of the fetus, and sometimes death. There was also a decrease in litter size (~3 compared to 8) with no bias in sex ratio (Mahendroo et al., 1996). In contrast, SRD5α2/KO female mice show normal gestation (Mahendroo et al., 2001). The parturition defect in SRD5α1/KO is mainly due to a lack of cervical ripening at gestational days 18–19, which is provoked by the lack of progesterone (P_4) degradation by SRD5α1 in the cervix (Mahendroo et al., 1999). The defect can also be related to a lack of 5α-reduced androgens (5α-DHT, 5α-androstenedione and 5α-androstane-3α,17β-diol) at the end of gestation, since their administration increases parturition success (33% to 93% with 5α-androstane-3α,17β-diol) (Mahendroo et al., 1996). However, the exact role of these 5α-reduced androgens remains unclear. In contrast, the reduction in litter size takes place between gestational days 10.75–11 and is provoked by the conversion of accumulated androstenedione and T into E_2 in the decidua (Mahendroo et al., 1997). Overall, those studies indicate SRD5αs are implicated in various biological functions during gestation that are additional to the development of secondary sexual organs in male fetuses. Future work should investigate how miscarriage and birth defects occur in females lacking SRD5α1 or SRD5α2.

3.2.2. Androgenic and estrogenic effects in female fish

In female fish, 5ARI treatments increased follicle atresia (Margiotta-Casaluci et al., 2013; Lee et al., 2015). In fathead minnows (*Pimephales promelas*), females also have a decrease in E_2 and an increase in T, which leads to a dramatic decrease in egg production (Margiotta-Casaluci et al., 2013). In contrast, administration of 5α-DHT led to ovotestis in females, and depending on the species, 5α-DHT can either increase or decrease the levels of E_2 and vitellogenin, a precursor of the egg yolk which is an estrogenic biomarker (reviewed in

Martyniuk et al., 2013). Hence, 5α-DHT appears to have both androgenic and estrogenic effects in female fish. The duality of response to 5α-DHT in fish could be linked to its conversion in 5α-androstane-3β,17β-diol, a steroid that has estrogenic capacity by interacting with the estrogen receptor β (Oliveira et al., 2007).

3.3. Brain development and behaviour: role of ALLO

Expression of *SRD5αs* occurs throughout the brain and is observed from early development (rat: Poletti et al., 1998; frog: Bruzzone et al., 2010; Bissegger and Langlois, 2016a) (Table 1). In the brain, mostly SRD5α1 is known to convert P_4 into 5α-dihydroprogesterone (5α-DHP). 5α-DHP is then transformed by the 3α-hydroxysteroid dehydrogenase (3α-HSD) into ALLO (Fig. 1B), an agonist of the neurotransmitter gamma-aminobutyric acid A receptor ($GABA_AR$) (Reddy, 2010). In the brain, the absence of SRD5α activity decreases ALLO levels (sheep: Yawno et al., 2007; rat: Modol et al., 2013; SRD5α1/KO mice: Koonce and Frye, 2013; guinea pig: Kelleher et al., 2011), while the concentrations of P_4 and T increase (rat: Darbra et al., 2013; Giatti et al., 2016), and 5α-DHT remains unchanged (rat: Giatti et al., 2016). The decrease in the neurosteroid ALLO increases anxiety-related behavior and convulsion in vertebrates, as well as impacting brain development.

3.3.1. ALLO decreases anxiety-related behaviour

Reduction of ALLO levels generates a less explorative behaviour and a more anxiety-related behaviour (rat: Darbra and Pallarès, 2010; Darbra et al., 2013; SRD5α1/KO: Frye et al., 2004; Koonce and Frye, 2013). The anxiety is reversed when ALLO is administered (SRD5α1/KO: Frye et al., 2013), but not when P_4 is administered (SRD5α1/KO: Frye et al., 2004; Koonce and Frye, 2013). These results show that the conversion of P_4 into ALLO is responsible for the anti-anxiety effects and is not due to other functions of P_4 in the brain. This correlates with observations in depressive patients, in whom ALLO brain levels are low and increase with antidepressant treatment (Uzunova et al., 1998; Agis-Balboa et al., 2014).

ALLO's function on anxiety is also implicated in females' receptiveness during reproduction. An increase in P_4 during proestrus in mice increases exploration and decreases anxiety (Koonce et al., 2012). Proestrus corresponds to the period in the ovarian cycle when female rodents are more sexually receptive, which they exhibit by a lordosis reflex, a dorsiflexion of the spine to facilitate copulation. In ovariectomized SRD5α1/KO mice, lordosis is less observed compared to their wildtype (WT) counterpart. Also, administration of ALLO, but not P_4, can rescue the phenotype (Koonce and Frye, 2014). ALLO's function during lordosis plays a role in the maintenance of lordosis, while E_2 is sufficient to induce lordosis (Uphouse, 2015). In order to maintain lordosis, ALLO binds to dopamine type 1-like and $GABA_AR$ in the ventral tegmental area of the brain (rat: Frye and Walf, 2008), in which SRD5α1 and/or SRD5α2 are expressed (Table 1). It would be interesting to see if ALLO is implicated in female sexual receptiveness in other species. For example, in vocal teleost fish and anurans, females show receptiveness with a behaviour called phonotaxis. Phonotaxis is a movement related to sound, in this case male vocalisation during courtship, and is correlated with season and sexual steroids (frog: Arch and Narins, 2009; Wilczynski and Lynch, 2011; fish: Forlano and Bass, 2011).

3.3.2. Anticonvulsant effect of ALLO

In mice, both P_4 and ALLO administration protects from pentylenetetrazole-induced seizures. However, when treated with FIN, only ALLO has anticonvulsant property and not P_4 (Kokate et al., 1999). In ovariectomized SRD5α1/KO mice (Frye et al., 2002a) and FIN treated male rats (van Luijtelaar et al., 2003), it is also observed that P_4 administration has no effect on seizure in contrast to control animals. These results show that the observed anticonvulsant property is due to ALLO and not to P_4. ALLO has anticonvulsant capacity in pentylenetetrazole-induced seizures, but not in maximal electroshock seizure tests (Kokate et al., 1999). The reason leading to a difference in response during different simulation of seizures is that ALLO acts as an anticonvulsant by competing for $GABA_AR$ against the pentylenetetrazole, which is an antagonist of the receptors that can generate epilepsy (Reddy, 2010). However, it cannot counteract seizures based only on electric discharge, like in the maximal electroshock seizure test.

3.3.3. Neuroprotection of fetal brain during late gestation

During late gestation, ALLO levels are elevated in foetal brain and decrease significantly after birth (sheep: Nguyen et al., 2003; guinea pig: Kelleher et al., 2013). While in the adult life, ALLO stimulates brain activity via $GABA_AR$; during gestation, data suggest that the activation of $GABA_AR$ with ALLO have the opposite effect by reducing fetal arousal. Inhibition of arousal with ALLO during pregnancy induces a sleep-like behaviour in the foetus, limiting fetal activity and oxygen consumption (Hirst et al., 2014). ALLO is also important to prevent apoptosis in the fetal brain (sheep: Yawno et al., 2007; Yawno et al., 2009) and to stimulate myelination of white matter neurons (guinea pig: Kelleher et al., 2011). These functions of ALLO seem to be mediated via the activation of oligodendrocytes (Hirst et al., 2014; Hirst et al., 2016) and can be critical during late gestation. Indeed, guinea pig preterm neonates exhibit reduced brain levels of ALLO (Kelleher et al., 2013). This means those preterm newborns would have increased apoptosis and decreased myelination in the brain which could lead to long-term deficits.

3.4. Aggressiveness in males: role of 5α-androstane-3α,17β-diol (3α-diol)

In the brain, 3α-diol is synthesized by the same enzymatic cascade as ALLO, but instead of using P_4 as the primary substrate, T is reduced subsequently by SRD5α and 3α-HSD (Fig. 1C). 3α-diol can have anticonvulsant properties like ALLO (SRD5α1/KO mice: Frye et al., 2001), but its main known function is its implication in aggressiveness patterns in males, which has mostly been studied in mice. In orchidectomized male mice, the number of aggressions registered against a new resident in the cage is increased by the administration of T and even more by 3α-diol (Frye et al., 2002b), showing 3α-diol has more potential than T to induce aggression. In SRD5α1/KO mice, T administration does not increase aggression in comparison to vehicle-administered control (Frye et al., 2002b), which suggests the conversion into 3α-diol is necessary to increase aggressiveness. Male SRD5α2/KO mice also show less aggressiveness, dominance over female, and risk-taking behaviours than WT mice (Mosher et al., 2018). The role of 3α-diol in aggressiveness indicates that even though a male is fertile, if it lacks 3α-diol, it will be less prone to defend its territory against other males, dominate females, and engage in intercourse, which will lead to a decrease in reproduction. Decrease in 3α-diol could also be related to the decrease in libido experienced by men taking 5ARIs (Liu et al., 2016; Corona et al., 2017). Moreover, 3α-diol is probably implicated in inhibiting brain feminization in males. Castrated rats exposed to FIN during gestation and treated with E_2 exhibit lordosis in contrast to untreated pups (Ribeiro and Pereira, 2005), a behaviour associated with females. More studies need to be done on 3α-diol and male reproductive behaviour and aggressiveness patterns across species, which are typically associated with androgens, precursors to 3α-diol. For example, in elasmobranch species, males with high levels of androgens perform aggressive courtship in which they assault the female and even bite her (Forlano and Bass, 2011). In anurans, androgens are linked to male vocalisation, which can act as advertisement call for females, as well

as territorial calls for nearby males (Wells, 1977; Wilczynski et al., 2005; Leary, 2009)

3.5. Effects on weight, steatosis, and insulin resistance

SRD5α1 is more highly expressed in the liver than *SRD5α2* (Table 1) and a lack of SRD5α1 activity generates a defect in glucocorticoid clearance. Indeed, adrenalectomised SRD5α1/KO mice have a decrease in corticosterone clearance after corticosterone administration (Livingstone et al., 2014; Livingstone et al., 2017). Also, men excrete less 5α-reduced metabolites of T and glucocorticoids in urine after starting 5ARI treatments (Upreti et al., 2014). The reduced clearance of glucocorticoids is not seen in the plasma levels of SRD5α1/KO mice (Livingstone et al., 2014; Livingstone et al., 2017), but rather on corticosterone levels present in the liver, which are elevated (Livingstone et al., 2017). Moreover, the response to adrenocorticotropic hormone is impaired (Livingstone et al., 2014) and genes related to regulation of hypothalamo-pituitary-adrenal (HPA) axis (vasopressin, glucocorticoid receptor, corticotropin-releasing hormone, and its receptor) are down-regulated in the liver (Livingstone et al., 2017), hypothalamus, and pituitary (Livingstone et al., 2014). Hence, slow clearance of glucocorticoid clearly interferes with the HPA axis.

A slower clearance also signifies that glucocorticoids have extended effects by accumulatingin the liversince 5α-reduction inactivates them and increases their polarity to ease their excretion (Carlstedt-Duke et al., 1977; Nixon et al., 2012). Regarding fat metabolism, glucocorticoid accumulation up-regulates triglyceride storage and cholesterol synthesis (SRD5α1/KO mice: Livingstone et al., 2015; Livingstone et al., 2017), while lipid mobilization and β-oxidation are down-regulated (men treated with DUT: Hazlehurst et al., 2016; SRD5α1/KO mice: Livingstone et al., 2015). The increase in fat storage and synthesis results in weight gain and steatosis, also known as fatty liver (men: Upreti et al., 2014; Hazlehurst et al., 2016; rat: Livingstone et al., 2015; SRD5α1/KO mice: Dowman et al., 2013; Livingstone et al., 2015; Livingstone et al., 2017). Those effects are observed mostly on high fat diets (Dowman et al., 2013; Livingstone et al., 2015; Livingstone et al., 2017) and are exacerbated in females regardless of the diet (Livingstone et al., 2017). The exacerbation of effects is suggested to be related to naturally low androgen levels in females, which makes SRD5α1 loss more impactful on glucocorticoids levels. Regarding glucose metabolism, glucocorticoid accumulation down-regulates gluconeogenesis (Livingstone et al., 2015), as well as insulin receptor expression, (Dowman et al., 2013) leading to insulin resistance and hyperinsulinemia (men: Upreti et al., 2014; Hazlehurst et al., 2016; rat and male SRD5α1/KO mice: Livingstone et al., 2015; female SRD5α1/KO: Livingstone et al., 2017). Hence, inhibition of SRD5α1 in the liver will increase risk of obesity, insulin resistance and nonalcoholic fatty liver disease by reducing glucocorticoids clearance.

3.6. Role of SRD5α3 in N-glycosylation

The first discovery of SRD5α3 was in hormone-refractory prostate cancer, where it is overexpressed (Uemura et al., 2008). To date, only two studies have shown the ability of human SRD5α3 to reduce steroids *in vitro* (Uemura et al., 2008; Titus et al., 2014), whereas hamster SRD5α3 lacks this activity (Chávez et al., 2015). More studies need to be done to confirm its capacity to reduce steroids; however, SRD5α3 seems to have other functions. In 2010, Cantagrel et al. showed that consanguineous families with a CHIME syndrome (ocular colobomas, heart defects, ichthyosiform dermatosis, mental retardation and ear defects or epilepsy) had mutations in the SRD5α3 sequence and exhibited a defect in N-glycosylation. They demonstrated that SRD5α3 has the capacity to reduce polyprenol into dolichol (Dol) (Fig. 1 D). When phosphorylated in the endoplasmic reticulum, Dol is then used as a lipid carrier for glycan precursor needed in protein N-glycosylation. This function in N-glycosylation classifies SRD5α3 mutations as a congenital disorder of glycosylation (CDGs) -type 1. Since the first discovery, other mutations have been found in SRD5α3, all leading to variation of the CHIME syndrome (Kahrizi et al., 2010; Morava et al., 2010; Gründahl et al., 2012; Kasapkara et al., 2012; Kara et al., 2014; Wheeler et al., 2016; Taylor et al., 2017). The origin of patients' symptoms was also explained with a mouse model. SRD5α3/KO mice can only live up to gestational day 12.5 before dying. Their lethality was due to the inability to undergo axial rotation and a ventral body wall defect at gestational day 8.5, as well as a dilated heart (Cantagrel et al., 2010), which corroborates the heart and brain defects observed in patients. Hence, the function of SRD5α3 seems to diverge from SRD5α1 and SRD5α2. This could be explained by the separate evolution of SRD5α3 from other members of the family since early eukaryotes (Langlois et al., 2010a), which led to a difference in domain related to SRD5α1 and SRD5α2 (hamster: Chávez et al., 2015). It would be necessary to verify the ability of SRD5α3 to reduce steroids and polyprenol in other species to ascertain the function of SRD5α3 across vertebrates.

4. Genomic and non-genomic pathways are involved in the regulation of *SRD5α* expression

Even though SRD5α1 and SRD5α2 can be found in the same tissues (Table 1), both isoforms are not expressed in the same cell types. For example, in the brain, *SRD5α1* is mostly expressed in glial cells (astrocytes, oligodendrocytes) (rat: Kiyokage et al., 2005; Castelli et al., 2013; mice: Kiyokage et al., 2014; fish: Mathieu et al., 2001), but can be found in neurons (mice: Agis-Balboa et al., 2006; fish: Mathieu et al., 2001) and gonadotroph cells of the anterior pituitary (rat: Yokoi et al., 1996), while *SRD5α2* is mostly restricted to neurons (rat: Pozzi et al., 2003; Castelli et al., 2013). The difference in expression of isoforms between cell types is related to various mechanisms described in this section, including, the regulation by transcription factor such as hormone receptors (Fig. 3) and by epigenetics such as methylation of CpG islands (Fig. 4).

4.1. Androgens drive tissue-specific regulation of SRD5αs

Unsurprisingly, *SRD5αs* are regulated by androgens that they help synthesize. All three isoforms are predicted to possess androgen response elements (AREs) in their promoter sequences (Flood et al., 2013). In the promoter of *SRD5α2*, there are two classes of AREs. One is a classic ARE with a palindromic repeat of AGAACA, which is functional and can also act as a progesterone response element (PRE) (Matsui et al., 2002). The second is a selective ARE constituted of a partial direct repeat of AGAACA (Kerkhofs et al., 2012). In the human promoter of *SRD5α3*, only one ARE was confirmed to be functional (Li et al., 2011). Even if each isoform possesses AREs in its promoter, their regulation by ARE is more complicated than the simple activation of AR by androgens. For instance, in human prostate cancer cell lines, 5α-DHT administration differentially regulates the expression of the three *SRD5αs* in each cell line (Li et al., 2011). Furthermore, in rat's prefrontal cortex, *SRD5α2* is upregulated by the administration of T and 5α-DHT in both sexes, while *SRD5α1* expression profiles exhibit a sexual dimorphism. In males, *SRD5α1* is down-regulated when treated with T and 5α-DHT. In contrast, *SRD5α1* is upregulated in females only after 5α-DHT treatment (Torres and Ortega, 2003). In T-treated rats, *SRD5α1* is negatively regulated in the testes, whereas *SRD5α2* is unaffected, but is overexpressed in the prostate (Pratis, 2003). All those results show that even though all three *SRD5α* possess AREs in their promoter, each isoform in each tissue is differentially regulated by androgens. The differential regulation is probably linked to co-regula-

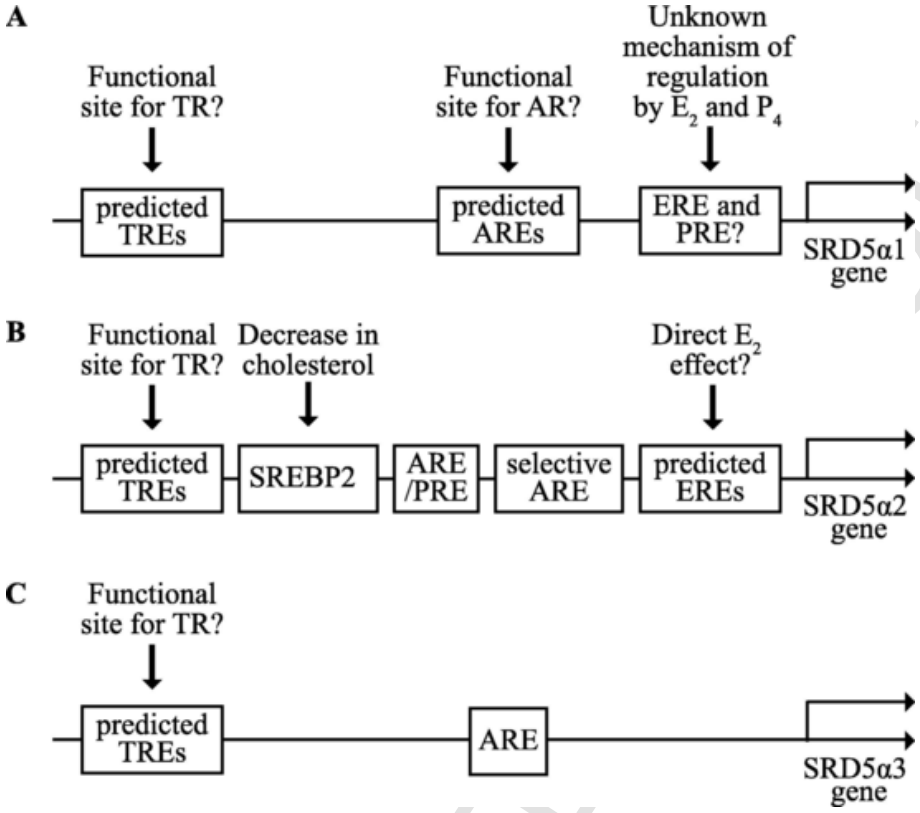

Fig. 3. Predicted response elements in the promoters of *SRD5αs*. (A) *SRD5α1* possesses TREs and AREs that are predicted, but have not yet been proven functional. Also, *SRD5α1* can be regulated by E_2 and P_4, but no study has looked at the presence of response element of those hormones in *SRD5α1*'s promoter; (B) *SRD5α2* can be regulated by androgens via two AREs. The first one is a classic ARE, which also acts as a PRE. The second one is a selective ARE, which is specific to only androgens. When cholesterol is low, SREBP2 upregulates *SRD5α2*. Finally, E_2 can also regulate *SRD5α2*, but it is yet unclear if it acts directly via a response element or indirectly by other pathways; (C) *SRD5α3* possess an ARE in its promoter, as well as predicted TREs, which the functionality remains unknown. The figure is a scheme and is not representative of the order, position, or the number of each response elements found in the genome. AR: androgen receptor; ARE: androgen response element; E_2: estrogen; ERE: estrogen response element; P_4: progesterone; PR: progesterone receptor; PRE: progesterone response element; SREBP2: sterol regulatory element binding proteins type 2; TR: Thyroid hormone receptor; TRE: thyroid response element.

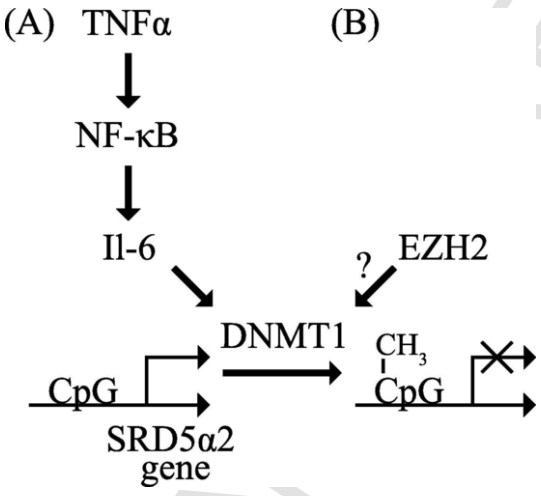

Fig. 4. Known mechanisms of methylation of CpG Island in the promoter of *SRD5α2*. (A) Inflammation cascade of TNFα, NF-κB and Il-6 which regulates the expression of DNMT1; (B) With age, EZH2 can regulate DNMT1 by an unknown pathway. DNMT1 methylates *SRD5α2*'s promoter and inhibits its transcription. DNMT1: DNA methyltransferase 1; EZH2: enhancer of zeste homolog 2; Il-6: Interleukin 6; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; TNF-α: tumor necrosis factor-α.

tors of AR, such as the pioneer factors (Pihlajamaa et al., 2015). Pioneer factors are able to bind to condensed chromatin and in turn help transcription factor like AR to bind it. The interaction between pioneer factors and AR is known to be tissue specific. For example, Forkhead box protein A1 (FOXA1) is a pioneer factor of AR specific to the prostate, while the hepatocyte nuclear factor 4 α (HNF4α) is specific to the kidney and the activating enhancer binding protein 2 α (AP-2α) to the epididymis (Pihlajamaa et al., 2014). It would be interesting to study how co-regulators, such as pioneer factors, regulate *SRD5αs* across tissues in combination with AR expression.

4.2. Progesterone and estrogen regulate SRD5αs in females

In addition of being the precursor of ALLO, P_4 has the ability to regulate the expression of *SRD5α2*, as shown by an increase of *SRD5α2* in the hypothalamus of female mice after P_4 administration (Matsui et al., 2002). To increase the expression of *SRD5α2*, P_4 binds to its receptor and activates *SRD5α2*'s transcription via the PRE, which has a common consensus sequence with the ARE found in *SRD5α2*'s promoter (Matsui et al., 2002). However, P_4 also appears to need the simultaneous action of E_2 to achieve regulation of *SRD5αs* in the body. As discussed earlier, P_4 and E_2 produced by females during proestrus play an important role in females' sexual receptiveness (Koonce et al., 2012). Moreover, *SRD5α1* expression and activity in mice uterus is increased by the administration of both P_4 and E_2 simultaneously, but not separately (Minjarez et al., 2001). The mechanism by which E_2 regulates *SRD5αs* is still mainly unexplored. Estrogen response elements (ERE) have been predicted in the promoter sequence of *SRD5α2* (Seenundun and Robaire, 2005; Campbell and Langlois, 2018), but their functionalities have not been assessed as of now. It could also be possible that E_2 acts via indirect pathways to help P_4 regulate *SRD5αs*. Further studies should elucidate the molecular mechanism by which P_4 and E_2

regulate *SRD5αs* to improve our understanding of the role of *SRD5αs* in females.

4.3. Cholesterol upregulates SRD5α2 levels

Inhibition of cholesterol synthesis and intake lead to an increase in expression of *SRD5α2* in the liver and the prostate of mice. This increase is generated by the sterol regulatory element binding proteins type 2 (SREBP2), a transcription factor, which has a binding site in the promoter of *SRD5α2* (Seo et al., 2009). SREBP2 is conserved across species and is implicated in cellular lipid homeostasis and cholesterol metabolism regulation when cholesterol levels are low (Jeon and Osborne, 2012). This indicates SRD5α2′s functions are important and should be conserved even when the body is low in cholesterol levels. Future work should investigate if other isoforms are also regulated by SREBP2 to further explore that type of regulation.

4.4. Thyroid hormones and androgens crosstalk

Thyroid hormones (THs) are known to cross-regulate androgens. For example, hypothyroidism can decrease androgens, LH, and gonadotropin-releasing hormone levels, (rat: Chiao et al., 1999; Kala et al., 2002; bird: Weng et al., 2007; fish: Swapna et al., 2006), impair testicular development (rat: Wagner et al., 2008; Maran, 2009), induce atrophy of epididymis and seminiferous tubules, decrease sperm number and motility (rat: Anbalagan et al., 2010; bird: Weng et al., 2007; fish: Swapna et al., 2006), and can even lead to a female biased sex ratio (frog: Goleman et al., 2002; fish: Mukhi et al., 2007). In the case of *SRD5αs*' regulation, a lack of THs decreases *SRD5α1* in all regions of rat epididymis and increases *SRD5α2* levels in corpus and cauda of the epididymis, but decreases it in the caput (Anbalagan et al., 2010). Moreover, administration of the thyroid hormone triiodothyronine (T3) in *S. tropicalis* can increase *AR*, *SRD5α1,* and *SRD5α2* (Duarte-Guterman et al., 2010; Duarte-Guterman and Trudeau, 2011) and *ex vivo* exposure of testes to T3 increases 5α-DHT (Campbell and Langlois, 2018). This cross-regulation of *SRD5αs* by TH can be explained by predicted thyroid hormone response element (TRE) in the promoter of each *SRD5α* isoforms (Flood et al., 2013). However, the functionality of those TREs still remains to be tested to ascertain their direct role in the regulation of *SRD5αs*. Moreover, another important aspect in TH regulation is the existing crosstalk with androgens due to the presence of ARE in genes related to THs, such as deiodinases and TH receptors (reviewed by Flood et al., 2013). Indeed, 5α-DHT treatment increases transcription of thyroid receptor β and deiodinase 1 (Campbell and Langlois, 2018), and FIN treatment impacts expression of TH-related genes such as deiodinase and TH receptors in *S. tropicalis* (Langlois et al., 2010b; Langlois et al., 2011). Therefore, THs are a major pathway of regulation for *SRD5αs* and should be explored further to understand THs implication in male development.

4.5. Age- and tissue-specific methylation patterns of SRD5αs' promoter

Patterns of methylation of *SRD5αs* are established during early development. In *S. tropicalis* embryos, methylation of *SRD5α2′*s promoter is detected beginning at the two-cell stage, which suggests the methylation occurred in the germ cells of parents before or during fertilisation. In contrast, the promoters of *SRD5α1* and *SRD5α3* are lowly methylated at the two-cell stage and get methylated around stage Nieuwkoop-Faber 13 (NF13) (Bissegger and Langlois, 2016a), which corresponds to the beginning of the neurula (Nieuwkoop and Faber, 1994). This early methylation of genes leads to a differential methylation pattern of *SRD5αs* across tissues. In male rats, *SRD5α1* is mildly methylated in testes, epididymis, and liver, while *SRD5α2* is highly methylated in liver and less in testes and epididymis (Reyes et al., 1997). This differential methylation of *SRD5αs* correlates with the more ubiquitous expression of *SRD5α1* across tissues and the more specific expression of *SRD5α2* in male sexual tissues (Table 1).

The methylation of CpG islands affects gene transcription by preventing transcription factors from binding to promoters. For example, methylation of CpG islands in *SRD5α1′*s promoter inhibits the binding of specific protein 1 (Sp1), a transcription factor, which in turn prevents the transcription of *SRD5α1* (Blanchard et al., 2007; Araki et al., 2015). Similar effects of methylation on transcription are expected for SRD5α2 since its promoter also possesses a Sp1 binding site (Matsui et al., 2002; Seenundun and Robaire, 2005). It is also expected that methylation may affect other transcription factors involved in the regulation of *SRD5αs* discussed earlier such as AR and TH receptor.

Through life, methylation patterns of *SRD5αs* can be modified. One factor that can act on *SRD5αs*' methylation is age. Indeed, *SRD5α2* is one of the most differentially methylated genes with age in mice and human liver (Mozhui and Pandey, 2017). In older BPH patients, *SRD5α2′*s promoter is more likely to be methylated in the prostate (Bechis et al., 2015; Ge et al., 2015). Moreover, those methylation patterns can be replicated in the prostate of old mice (Ge et al., 2015). Also, *SRD5α1′*s expression decreases with age in the hippocampus of rats, which correlates with increased methylation (Rossetti et al., 2015; Rossetti et al., 2016; Rossetti et al., 2019). A second factor that can increase methylation is inflammation linked to disease. Up to 36.5% of patients with BPH exhibit a decrease in *SRD5α2* expression linked to hypermethylation of its promoter, which renders FIN therapy useless (Niu et al., 2011; Ge et al., 2015; Horning et al., 2015). This increase in methylation is connected to inflammation generated by the tumor necrosis factor-α (TNF-α) (Ge et al., 2015; Wang et al., 2017). Another factor leading to a change in methylation is mental health and stimulation. Enrichment of the environment can help decrease methylation of *SRD5α1′*s promoter in the hippocampus of rats (Rossetti et al., 2015; Rossetti et al., 2019), while social isolation will increase its methylation in the prefrontal cortex of mice (Araki et al., 2015). Additionally, patients who went through FIN withdrawal and developed depression and anxiety problems exhibit high methylation of *SRD5α2′*s promoter (but not *SRD5α1′*s) in their cerebrospinal fluid (Melcangi et al., 2019).

Several mechanisms leading to a change in methylation pattern of *SRD5αs* have been found (Fig. 4). One of the mechanisms is a pro-inflammatory cascade induced by the tumor necrosis TNF-α, which repress the expression of *SRD5α2* in BPH patients (Ge et al., 2015; Wang et al., 2017). TNF-α activates a cascade composed of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and interleukin-6. The activation of this cascade leads to the expression of DNA methyltransferase 1 (DNMT1), which binds to *SRD5α2′*s promoter and methylates its CpG islands (Ge et al., 2015). Methylation can also be regulated by the enhancer of zeste homolog 2 (EZH2), a member of the polycomb repressive complex, which increases methylation of *SRD5α2′*s promoter with age (Mozhui and Pandey, 2017). However, the exact mechanism by which EZH2 activates DMNT is still unclear and should be studied further.

5. Conclusion

As seen in this review, SRD5αs are implicated in various essential biological functions. SRD5α2 is mostly involved in the synthesis of 5α-DHT, a potent androgen necessary for the development of male urogenital tract, as well as the maintenance of male sexual organs' function throughout adulthood such as erectile function and sperm maturation. 5α-DHT also seems to play a role in hormonal sex determination of amphibians, while its role remains ambiguous in fish where 11-KT is the most potent androgen. In the brain, SRD5α1 is involved in the production of ALLO and 3α-diol, two neurosteroids. Both are known

to have anticonvulsant properties and play a role in reproductive behavior. Additionally, ALLO can reduce anxiety and increase myelination during development. This review also highlighted two largely unexplored functions of SRD5αs. The first one is the function of SRD5α1 and possibly SRD5α2 in the degradation of steroids in the uterus such as P_4, which can otherwise prevent parturition. The second is the role of SRD5α1 in glucocorticoid clearance in the liver which helps prevent metabolic syndrome by reducing the half-life of glucocorticoids. Furthermore, this review shows that since the discovery of the role of SRD5α3 in N-glycosylation by producing dolichol, little research has been done to clarify the function of SRD5α3 in steroid reduction and even its ability to do so. Finally, this review has reported the known mechanism of regulation of *SRD5αs* by hormone receptor and methylation of CpG islands. However, more studies must be done to draw a better picture of their regulation from fertilization to adulthood, as well as exploring other molecular mechanisms of regulation such as the implication of pioneer factors or histone modifications.

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Declarations of interest

None.

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