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Steroid Hormone Receptors and Male Reproductive Health: From Functional Role(S) To Endocrine Disruption

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ABSTRACT:

The deterioration of male fertility during the last decade is of prime concern. One of the possible reasons could be environmental pollutants with endocrine-disrupting properties. These chemicals can able to mimic, block or interact with endogenous hormones and their cognate receptors; they can interfere with endocrine mediated reproductive functions. However, the mechanisms are unknown. Steroid hormones such as androgens, estrogens and glucocorticoids play a crucial role in the regulation of male fertility and they exert their genomic actions via steroid hormone receptors. In order to gain possible insights into the mechanism of action of endocrine disrupting chemicals (EDCs) on male reproductive health, we summarize the current understanding of the effects of EDCs that interfere with steroid hormone receptors in mammals. The knowledge gained could be helpful to develop strategies to mitigate the negative impacts of environmental pollutants on male reproductive health.

Introduction:

Published studies have shown that the fertility issues are a concern for many couples around the world and the estimates of World Health Organization indicated that around 8% to 12% of couples are affected by primary infertility, which translates to a range of 48 million to 186 million individuals worldwide[1]. During the past five decades an increase in the congenital male reproductive disorders such as cryptorchidism, hypospadiasis, testicular cancer and testicular dysgenesis associated with reduced sperm density and quality has been reported[2-18]. As a result of these male reproductive disorders there has been a decrease in the quality and quantity of sperms resulting in male infertility[19]. Though mechanisms have yet to be defined, a range of chemicals with diverse properties can have profound effects on human health including endocrine mediated functions[20]. It has been shown that humans and wildlife exposed to chemicals with endocrine disrupting properties resulted in reproductive and developmental abnormalities, cancer, immune system dysfunction, and failure of vital organs such as brain, liver, kidneys and lungs[21,22]. It is well known that some chemicals attain ability to a) behave like endogenous hormones and accordingly bind their cognate receptors, b) block the action or inhibit the synthesis of endogenous hormones and c) modify the production and function of receptors and d) inhibit the synthesis and secretion of endogenous hormones. Therefore, such substances with endocrine disrupting properties are termed as endocrine active agents or endocrine disrupting chemicals (EDCs). Studies indicated that the major routes for the EDCs seems to be sewage effluents and improper treatment of wastewater from pharmaceutical, metal, pesticide and cosmetic industries which eventually reach large aquatic bodies and contaminate potable water. Some common sources of EDCs include certain chemicals used in industry, such as certain plastics (e.g. bisphenol A or phthalates)[23,24] and flame retardants (e.g. polybrominated diphenyl ethers or PBDEs)[25], as well as pesticides used in agriculture (e.g. organochlorine, organophosphates, pyrethroids, and carbamates)[26-29]. Therefore, it is conceivable that EDCs can able to interfere with hormone-mediated processes thereby interfere with a broad array of physiological events. It is well established that the male reproduction is one of the endocrine controlled processes and thus, a susceptible target for EDCs[12,16-18]. However, the exact underlying mechanism(s) of EDCs on

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male reproductive health is not well defined and this could be ascribed to the fact that the male reproduction is regulated by multiple factors.

The present review does not focus on the basics of the toxicants or is not intended to be exhaustive on their generally known mechanisms of action, since this information can be available in several recent reviews. Instead, we summarize the effects of several toxicants with endocrine disrupting properties on steroid hormone receptors and the consequences of their interactions on testicular functions and male fertility efficacy. The current information might be used as a tool to develop therapeutic strategies to protect male reproductive health against chemicals with endocrine disrupting properties[30,31].

In view of the aforementioned data, the present review deals with the following aspects: 1) the first aspect deals with endocrine regulation of spermatogenesis and steroidogenesis; 2) the second aspect deals with endocrine disrupting chemicals that interfere with steroid hormones and their cognate receptors; 3) finally, we discuss the gaps and challenges that needs to be addressed.

Endocrine regulation of male reproduction

In mammals, the structural and functional integrity of male reproductive tract (a pair of testes, and other accessory sex components like epididymis, vas deference, seminal vesicles, prostate gland and a penis) is controlled and coordinated by a variety of exocrine and endocrine factors and proper functioning of these organs is crucial for fertility efficacy[32]. Male gamete is one of the determinants of fertility and thus, the main function of male reproductive system is to produce, store, nurture and transfer the sperm and protecting the seminal fluid. Testis is the major reproductive organ and performs two important functions: production of sperm (male gamete): spermatogenesis and production of androgens: steroidogenesis, while epididymis, an accessory sex organ is involved in post-testicular sperm maturation events, a key factor for a sperm to acquire fertilizing ability. A range of diverse endocrine factors, control and coordinate spermatogenesis, sperm maturation events and steroidogenesis in mammals. It is well established that the hormones produced and secreted by the hypothalamic-pituitary-testicular (HPG) axis regulate the male reproductive tract functions. Hypothalamus located beneath the thalamus synthesize a decapeptide known as gonadotropin releasing hormone (GnRH) which in turn stimulate the anterior part of the pituitary gland to produce gonadotropins. The pituitary gland is popularly known as master of endocrine glands as it regulates many of the biological functions of the body by its secretions produces two gonadotropins viz., follicle stimulating hormone (FSH) and luteinizing hormone (LH) which target the testicular Sertoli and Leydig cells, respectively. They exert their actions via leutinizing hormone chorionic gonadotropin receptor present on the Leydig cells and follicle stimulating hormone receptor present on the Sertoli cells[33]. The LH stimulation leads to the synthesis of testosterone production from its percussor, cholesterol from the Leydig cells and LH regulates Leydig cell steroidogenesis by its cognate receptor[34]. On the other hand, the interplay between the FSH, testosterone and the Sertoli cells is considered important for spermatogenesis[35,36]. Moreover, FSH sustains the Sertoli cell number via its differentiation and proliferation in the testis and most strikingly, FSH-mediated regulation of structural genes of cell-cell junctions and genes that govern regulatory and nutritional factors from Sertoli to germ cells is well appreciated at the molecular level[33]. FSH is key player in the feedback mechanisms thereby regulation of testicular functions via HPT-axis[37]. The maturation of spermatogonia into mature spermatozoa is regulated by FSH via Sertoli cell functions. The number of Sertoli cells and their ability to support developing germ cells, thereby spermatogenesis is under the regulation of FSH[36]. In humans, fertility phenotypes in carriers of inactivating *fshr* mutations leads to reduction of spermatogenesis[38]. Therefore, an intact HPT axis is critical for testicular functions[33] and any disturbances may lead to infertility. For more information about the role of gonadotropins such as FSH and LH on male reproductive health[39-41].

Apart from gonadotropins, steroid hormones such as androgens, estrogens and corticosteroids are another set of endocrine factors that occupied a strategic position in the regulation of male reproductive health thereby fertility potential. Androgenic effects in the testis occurs via the testosterone produced by the Leydig cells, while such effects in the male reproductive tract occurs via dihydrotestosterone (DHT), the reduced and more potent form of testosterone. Androgens are key for secondary sexual characters and play essential role in growth and

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development of male reproductive tract functions like spermatogenesis and also involves in the feed-back regulation of secretion of pituitary hormones[42]. In response to testosterone and its metabolic product dihydrotestosterone mediate their genomic actions via androgen receptors and regulate the expression of target genes[43]. Estrogenic effects in testis occurs via estrogens and estradiol is believed to be one of the predominant forms of estrogens in men and is a key hormone in modulating libido, erectile function, and spermatogenesis. Studies have shown that both estrogen excess and estrogen deficiency influence male sexual development, testis function, the hypothalamic-pituitary-testis axis, spermatogenesis and ultimately male fertility[44]. Studies also indicated that an equilibrium between estrogen to testosterone ratio is considered important for proper functioning of physiological events in men45. Interestingly, glucocorticoids and mineralocorticoids belong to corticosteroids which exhibit either positive or negative effects on the fertility efficacy and depends on the timing, dose, and glucocorticoid-responsiveness within a given tissue. It is believed that steroid hormones exert their effects at least in part via nuclear receptors. The genomic actions of androgens, estrogens and corticosteroids occurs via ligand-inducible transcriptional factors known as nuclear receptors. Androgens act as ligands for androgen receptors, estrogens via estrogen receptors (ER), and corticosteroids via glucocorticoid (GR)/mineralaocorticoid (MR) receptors respectively and exert their genomic effects. The classical genomic mechanism of steroid hormone signalling occurs when they diffuse into the cell and binds to their cognate steroid hormone receptor and eventually translocation of ligand–receptor complex to the nucleus followed by their binding to response elements in the regulatory regions of genes to modify their translation.

Published reports have shown that the EDCs can interfere with steroid hormone receptors thereby exert adverse effects on male reproductive health[46]. In the next section, we focus on an overview of structural aspects of NRs followed by steroid hormone receptors.

Steroid hormone receptors

Regulation of gene circuits is one of the major events in each and every cell and the response induced by the gene circuits differ from one tissue to another, wherein such genomic actions are mediated via ligand-induced transcriptional factors, known as nuclear receptors (NRs)47. NRs are a unique superfamily of 48 transcription factors and in humans, they regulate a wide range of processes, including development, circadian rhythms, endocrine and metabolic fluxes, behavior, and also xenobiotic stress[48]. NR defined distinct regulatory decisions seems to be nuanced and comprise the allosteric transmission of ligand-induced conformational changes in the ligand-binding domain (LBD) to the closely juxtaposed DNA-binding domain (DBD). In each case, the allosteric signals are transmitted through a convergence zone formed between DBD and LBD interface. Studies have shown that the malfunctioning of NRs may cause a wide array of diseases and inherited disorders[49].

Based on key characteristics, NR superfamily is broadly categorized into four major classes wherein class I NR family includes steroid receptors, class II NR family includes RXR heterodimers, class III family includes orphan receptors and class IV family includes monomeric orphan receptors. Though, they share certain Class I to III NRs require dimerization (class I and III NRs require homodimerization, while class II NR exert its actions via formation of heterodimers) for their signaling mechanisms, whereas dimerization process is not required for class IV NRs (**Fig. 1**). The structure of NRs comprised of A/B, C, D, E domains wherein A/B domain is located at N-terminal end, while D domain acts as a hinge region between C (DNA Binding domain: DBD) and E (Ligand Binding domain: LBD) domains. A/B domain of NRs is a

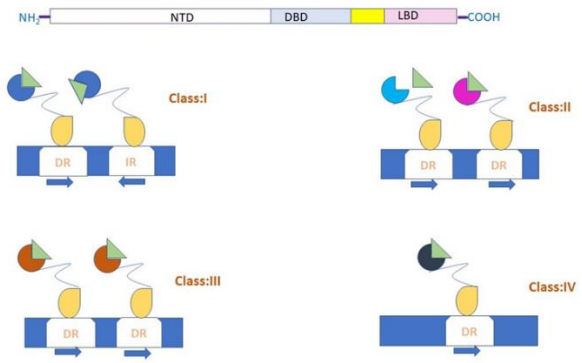

Figure 1: The figure depicts four major classes of nuclear receptors: Class I, Steroid Receptors; Class II, retinoic acid x receptor (RXR) Heterodimers; Class III, Dimeric Orphan Receptors; and Class IV, Monomeric

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Orphan Receptors. The classification of nuclear receptors is based on dimerization, DNA binding: direct or inverted repeats and Ligand specificity: required or not required. The illustration includes abbreviations for various domains: NTD (N-terminal domain), DBD (DNA-binding domain), H (Hinge region), LBD (Ligand-binding domain), C (Variable C-terminus), DR (Direct Repeat), and IR (Inverted Repeat).

structurally diverse and often intrinsically disordered region and is typically composed of approximately 100-400 amino acids. One of the key functions of the NTD is to mediate the transcriptional activity of the receptor through its activation function 1 (AF-1) region. The AF-1 region is a transcriptional activation domain that recruits coactivator proteins, leading to the initiation of transcription of target genes. The AF-1 region interacts with various coactivators, such as p300/CBP, SRC-1, and GRIP-1, which contain LXXLL motifs[50-52]. The LXXLL motif is a protein-protein interaction motif that is conserved across several transcription factors and coactivators. It mediates the interaction of these proteins with the NTD of nuclear receptors, facilitating the recruitment of coactivators to the receptor, and the subsequent initiation of transcription. N-terminal domain of NR also contains the dimerization interface that facilitates the homodimerization and heterodimerization of nuclear receptors. The dimerization interface is involved in the formation of the active receptor complex, which binds to DNA response elements and regulates the transcription of target genes. The NTD also contains several protein-protein interaction motifs, such as FXXLF and LXXLL, which mediate the interaction of the receptor with other transcription factors and coactivator proteins. The FXXLF motif is a protein-protein interaction motif that is involved in the interaction of the receptor with the steroid receptor coactivator-1 (SRC-1) and other coactivators[53,54]. The proline-rich motif found in the NTD of nuclear receptors is known to interact with the SH3 domains of various signaling proteins. This interaction can serve as a molecular switch that regulates the activity of these proteins and contributes to diverse cellular processes, such as cell growth, differentiation, and survival[55].

The DNA-binding domain (DBD) of NRs is typically composed of around 70-80 amino acids and is a structurally conserved region of the protein. The DBD is composed of two zinc fingers, each of which has an alpha-helix and a beta-sheet held together by four cysteine residues, which coordinate a zinc ion. The spacing between the cysteine residues in the zinc fingers allows them to interact with specific DNA sequences in the major groove of the DNA helix[56]. The first zinc finger of the DBD is known as the P-box, while the second zinc finger is known as the D-box. The P-box interacts with the first three base pairs of the hormone response element (HRE) sequence, while the D-box interacts with the next three base pairs, responsible for protein – protein interactions[57]. The specific sequence recognized by the DBD can vary depending on the specific nuclear hormone receptor, but it typically consists of a palindromic or semi-palindromic sequence of 6-8 base pairs[58]. NRs commonly control the expression of genes by binding to DNA response elements that are associated with their target genes and these response elements are made up of six nucleotides arranged as direct or inverted repeats and consist of half-sites with the sequence 5′AGAACA3′ or 5′AGGTCA3’[59].

The hinge region of NRs is a flexible and highly variable region that connects the DNA-binding domain (DBD) and the ligand-binding domain (LBD) of the receptor[60]. It is typically composed of approximately 30-60 amino acids and has a low sequence conservation across the nuclear receptor family. Despite its low sequence conservation, the hinge region plays an important role in regulating NR function. It contains several phosphorylation sites that are regulated by various cellular signaling pathways and can modulate the interaction between the DBD and the LBD. Phosphorylation of the hinge region has been shown to regulate NR activity, stability, and subcellular localization[61] .

The ligand-binding domain (LBD) of NRs is a structurally complex and highly conserved region of the protein that plays a critical role in regulating gene expression. The LBD is typically composed of around 250-300 amino acids and is responsible for binding to specific ligands, such as hormones, and recruiting coactivator or corepressor proteins to the transcriptional complex. The LBD consists of 12 alpha-helices and 4 beta-strands, which together form a three-dimensional structure known as a "folded-up helix." This folded-up helix is highly conserved across the nuclear receptor family and plays a critical role in ligand binding. The

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LBD also contains a highly flexible loop region, which is referred to as the "AF-2 domain," that is important for mediating interactions with coactivator or corepressor proteins[62].

The ligand-binding pocket of the LBD is composed of several hydrophobic amino acids and can accommodate a wide range of ligands, including small molecules, peptides, and lipids. The specificity of ligand binding is determined by the shape and size of the ligand-binding pocket, as well as by specific interactions between the ligand and amino acid residues within the pocket. Upon ligand binding, the LBD undergoes conformational changes that allow it to recruit coactivator or corepressor proteins to the transcriptional complex. Coactivator proteins interact with the LBD through a conserved LXXLL motif, which allows them to bind to the AF-2 domain and stabilize the active conformation of the LBD[53]. Corepressor proteins, on the other hand, interact with the LBD through a conserved NR box motif, which allows them to bind to the AF-2 domain and stabilize the inactive conformation of the LBD[63].

Despite of significant structural and functional differences, some structural components of NRs are preserved which seems to be permissive to exert their respective genomic actions. In the next section, we only emphasize on class I NRs (steroid hormone receptors) and for more information on NRs these excellent reviews may be referred[64,65].

Steroid hormone receptors

Steroid hormone receptors including androgen receptor (AR), estrogen receptor (ER), progesterone receptor (PR), glucocorticoid receptor (GR), and mineralocorticoid receptor (MR) are commonly referred to Class-1 NRs. All the class I steroid NRs exhibit common structural components of typical NRs domains: A/B, C, D, E domains with differences in their sequences and binding abilities to their respective ligands. The A/B, C (DBD) and E (LBD) domains of ER alpha (15%, 51% and 20%, respectively), ER beta (15%, 56% and 22%, respectively), PR alpha (15%, 80%, and 52%, respectively), PR beta (15%, 80% and 53%, respectively), GR (15%, 77% and 50%, respectively), and MR (15%, 77% and 52%, respectively) exhibit sequence similarity of 15 % against AR. These receptors are activated by specific steroid hormones, such as testosterone (AR), estrogen (ER), progesterone (PR), cortisol (GR), and aldosterone (MR), respectively. The ability of steroid hormone receptors to modulate gene expression in response to their respective steroid hormones is crucial for maintaining homeostasis and coordinating the body's response to changing environmental and physiological conditions. Dysregulation of steroid hormone receptor signaling can lead to a variety of diseases, including cancer, metabolic disorders, and reproductive disorders (**Fig. 2**).

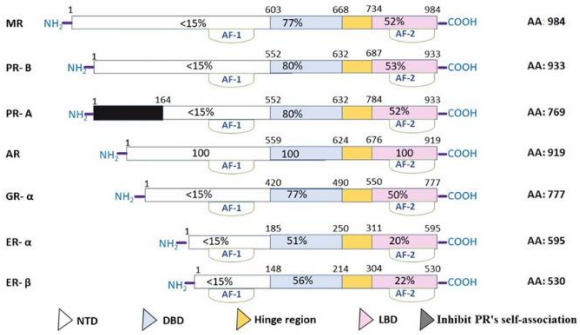

Figure 2: A schematic illustration depicting the percent identity in primary sequence of steroid hormone receptors compared to the androgen receptor

Androgen receptor (AR)

Androgens including testosterone (T) and dihydrotestosterone (DHT) that are important for structural and functional integrity of male reproductive tract functions. It is well known that T can undergo a transformation into its more potent form, DHT, through a process known as 5α reductase conversion. It can also be converted into oestradiol by the enzyme aromatase. Both T and DHT exert their effects through the AR, a type of transcription factor that is activated by binding to its ligand[66,67]. Androgens, through their interaction with the androgen receptor (AR) located on the X chromosome, have been shown to impact a variety of bodily systems, including bone, muscle, prostate, adipose tissue, the reproductive system, cardiovascular system, immune system, nervous system, and blood system[68]. Expression of androgen receptors (ARs) has been observed in various male reproductive organs, such as efferent ductules, urogenital sinus, Wolffian ducts, epididymides, ductus deferens, seminal vesicles, coagulating glands, prostates, and bulbourethral glands, starting from embryonic Day 13 to Postnatal Day 10[69,70.

The AR is a protein that is encoded by the AR gene, and it is composed of 919 amino acids[71]. The AR protein is

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composed of several functional domains including N-terminal domain, DNA-binding domain (DBD), and the ligand-binding domain (LBD). The N-terminal domain, DNA-binding domain, and ligand-binding domain work together to allow the AR to bind to androgens, bind to androgen response elements in DNA, and regulate gene expression[72]. AR is expressed in various testis tissues and all types of somatic cells, but is absent from germ cells. This highlights the need for T, a crucial factor for sperm production, to be mediated by signaling in somatic cells. By selectively eliminating AR from specific somatic cell types, researchers were able to determine the role of AR signaling in each cell type. It was found that AR signaling in Sertoli cells plays a significant role in supporting postmeiotic germ cell development, as well as in regulating the size of the Leydig cell population. Additionally, AR signaling in Peritubular myoid cells was found to support all stages of spermatogenesis and Sertoli and Leydig cell function. Lastly, AR signaling in Leydig cells was found to be crucial for the maturation of the Leydig cell population and its function in adulthood[73].

Estrogen receptors:

Estrogens are a type of steroid hormone that encompasses three hormones: estrone (E1), (E2, or 17β-estradiol), and estriol (E3). Among the estrogens, 17β-Estradiol, the most effective estrogen that control and coordinate various physiological processes including the growth and up keep of reproductive organs. Though primarily, estrogens are believed to be female hormones, the role of estrogens in male reproductive health has also been demonstrated74. Estrogens exert their actions via both nuclear and membrane receptors wherein ERα (estrogen receptor alpha) and ERβ (estrogen receptor beta) belongs to NRs and GPER1 (G protein-coupled estrogen receptor 1), also known as GPR30 is categorized under membrane receptors[75]. ERα and ERβ are expressed in various tissues and cells in both males and females, but the expression levels can vary depending on the tissue type and sex. With regards to the male reproduction, the expression of ERs is commonly found in the testis, efferent ductules, and epididymis of most species. The expression of ERα in testicular Leydig cells in adult men has been documented, while ERβ has been documented in both Leydig and Sertoli cells and efferent ducts[76]. On the other hand, ERβ and aromatase are expressed in Sertoli, Leydig, and germ cells of male fetus[77,78] but ERα is absent[79]. Studies also indicated that ERα has been detected in the nuclei of epithelial cells in the caput of the epididymis[80], while both ERα and ERβ have been identified in isolated immature germ cells[81] and also in human ejaculated spermatozoa[82]. In rodents, ERα is expressed primarily in the Leydig cells and in the proximal reproductive ducts and ERβ is expressed in both Leydig and Sertoli cells, as well as in the efferent ducts and some germ cells[83-85]. Published reports also indicated that ERβ is more highly expressed in the prostate, bladder, and immune system[86,87].

The Erα (595 amino acids) and ERβ (530 amino acids) are encoded by ESR1 and ESR2 genes, respectively and is composed of 595 amino acids[88-90] . They ERα and ERβ can also form heterodimers on estrogen response elements (EREs). With regards to sequence similarity, ERβ has a high degree of homology to ERα in the DNA-binding domain (DBD), with more than 95% of the amino acids being identical. The ligand-binding domain (LBD) of ERβ also has a moderate level of homology to ERα, with approximately 55% of the amino acids being similar. However, the N-terminal domain (NTD) of ERβ is shorter than that of ERα and has very limited similarity, with only around 15% of the amino acids similar to ERα's NTD[91-94]. The hinge regions of ERα and ERβ have limited homology, with only 36% of the amino acids being similar. On the other hand, the amino acids from 223 to 343 in ERα and from 404 to 457 in ERβ exhibit a more significant similarity than the sequence located between 223 to 457 in ERα and 344 to 403 in Erβ.

Progesterone receptor (PR)

Progesterone is a vital hormone that plays a significant role in the female reproductive system, especially in the menstrual cycle and pregnancy. Its ability to bind with progesterone receptors within cells allows it to regulate a wide range of physiological processes, including ovulation, uterine and mammary gland growth, and sexual responsiveness[95,96] . PR is expressed various tissues including uterus, ovary, vagina, breast, hypothalamus, pituitary gland, and adrenal cortex, liver, kidney, lung, skeletal muscle, and fat tissues. PR expression has also been reported in various human tissues, including the prostate and testis[97]. Thus, wide expression of PR directly correlates to its diverse and complex functions of progesterone and its role in regulating a wide range of physiological processes in mammals[98-101]. PR comprised of 933 amino acids and

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occurs in two forms: PRA and PRB[102]. Though, they share high sequence similarity, 164 amino acids present at the N-terminal end of PRB is missing in PRA[103] which in turn reflect in their differential transcriptional activation and repression functions. Further, 164 N-terminal domain extra amino acids in PRB can able to inhibit PR's self-association[104]. Furthermore, the AF1 region located in N terminal region of PRA exhibits a strong transactivation function and is capable of activating gene expression by interacting with co-activators and chromatin remodeling enzymes, whereas, AF2 domain in PRB seems to be a potent repression function and can able to inhibit gene expression by recruiting corepressor proteins[105].

Glucocorticoid receptor (GR) and Mineralocorticoid receptor (MR)

Glucocorticoids are a class of steroid hormones and are believed to be stress response hormones and are orchestrated by the hypothalamic-pituitary-adrenal (HPA) axis[106-108] . They control and coordinate physiological events like metabolism, stress response, cell growth, inflammation, immunity, development, and reproduction[109]. They exert their genomic actions via GRs[110] which are expressed in almost all human tissues and organs[111]. In humans, there are two forms of GR: hGRα and hGRβ which comprised of 777 and 742 amino acids respectively[112]. Studies have shown that GR in its unbound form to its ligand, heat-shock proteins (hsp90, hsp70, hsp90-binding protein p23), immunophilins ((eg, FKBP51, FKBP52, Cyp44, and PP5), bind GRs and protect it against degradation[113]. In the presence of ligand, the associated proteins are released from GRs thereby translocate to the nucleus, and interacts with co-regulators to enhance its transcriptional activity[114].

MRs (984 amino acids) are widely expressed in kidneys, heart, brain, adipose tissue and reproductive organs. The role of MR in the regulation of blood pressure in response to its ligand, aldosterone is well acknowledged[115]. With regards to male reproduction, MR activation causes erectile dysfunction[116]. The expression of MR has been reported in the epithelial cells of the epididymis, with higher expression levels in the caput than in the cauda epididymis[117]. The glucocorticoid receptor (GR) has a close relationship with the mineralocorticoid receptor (MR), and these receptors exhibit some overlap in their functions. The MR can be activated by its own ligands, known as mineralocorticoids, as well as by glucocorticoids, while the GR is only activated by glucocorticoids[118].

Distribution and Expression Patterns of Nuclear Receptors:

Steroid hormone receptors are mainly located in the cytoplasm and nucleus of target cells. In their inactive state, these receptors are usually present in the cytoplasm, bound to heat shock proteins[119]. When a specific hormone, like estrogen, testosterone, or cortisol, binds to the receptor, it undergoes a structural change, causing it to detach from the heat shock proteins and move into the nucleus. Once in the nucleus, the receptor attaches to specific DNA sequences known as hormone response elements, influencing the transcription of genes that regulate key physiological functions, including reproduction[120].

Androgen Receptors

Androgens are vital for sperm production, but germ cells themselves do not express functional androgen receptors (AR)[121]. Instead, AR in surrounding somatic cells regulates sperm production. AR is expressed in peritubular and Leydig cells from early fetal stages and continues after birth. In Sertoli cells, AR appears in the nucleus by 4–5 days after birth in mice, increases by 7–9 days, and remains active in adulthood[122]. While AR is strongly present in Sertoli cell nuclei, it is absent in germ cells like spermatogonia and spermatocytes[123].

Active AR localizes in the nucleus, while cytoplasmic AR is inactive[124]. In the classical pathway, androgens bind to AR, displace heat shock proteins, and move into the nucleus to regulate gene expression. In the non-genomic pathway, AR activates signaling cascades at the cell membrane, influencing processes like MAPK and ERK[125,126]. AR is also found in male reproductive organs such as the epididymis, seminal vesicles, prostate, and bulbourethral glands[69].

Estrogen Receptors

Estrogen receptors (ERs) are found at various stages of male reproductive development. In the fetal stage, ERβ and aromatase are expressed in Sertoli, Leydig, and germ cells[77,78], while ERα is absent[79].

After birth, in mice, ERβ expression peaks during postnatal days 1–5 and declines by day 12 [45]. In adult mice, ERβ is seen in Leydig and germ cells, but not in

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Sertoli cells[78] . ERβ is most prominent in pachytene spermatocytes and also found in spermatogonia, preleptotene spermatocytes, and round spermatids[123].In human development, ERα is present in Sertoli cells from childhood through puberty[127]. However, during puberty in mice, ERα levels begin to decline[128].

In adulthood, ERα is expressed in Leydig cells in men[76], and ERβ remains in Leydig and Sertoli cells, as well as the efferent ducts[76]. In human testes, ERα is absent, but ERα has been detected in the nuclei of epithelial cells in the caput region of the epididymis, while both ERα and ERβ are present in immature germ cells[77,81]. In human ejaculated sperm, both ERα and ERβ are expressed[82].

Progesterone Receptors

Research on progesterone receptor (PR) expression in male reproductive tissues shows mixed findings. In rats, PR-B, a specific isoform, is found in the testis at both the gene and protein levels[129]. In mice, PR knockout studies showed PR expression in Leydig cells when gonadotropin was suppressed, although this was based on a reporter line without immunohistochemistry confirmation[129]. In humans and primates, PR expression in the testis remains uncertain, with some studies showing widespread expression[130] and others indicating it is present in only a few cells[131].

Progesterone-binding sites have been observed in the testes of lower species, like immature rats[132]. PR is found in some peritubular and interstitial cells but not in germ cells. It is also expressed in the epididymis, prostate, and male mammary gland[131]. In human sperm, PR is located in the equatorial region of about 50% of sperm heads[133]. Additionally, PR expression has been noted in human prostate and testis tissues[97].

Glucocorticoid Receptors

Research on glucocorticoid receptor (GR) expression in the testis is less comprehensive compared to other tissues. In mice[134], GR expression has been detected in Leydig cells, peritubular cells, Sertoli cells, and early germ cells by postnatal day 20 . In adult mice, GR is present in the nuclei of spermatogonia and preleptotene spermatocytes but shows weak expression in pachytene spermatocytes and is absent in spermatids. In mature mice (70 days old), Sertoli cells do not express detectable levels of GR[134, 135].

In adult human testis, GR is observed in peritubular cells[136], Leydig cells, weakly in Sertoli cells, and in spermatogonia, but it is not present in spermatids. In fetal human testis, GR shows a different pattern, with heterogeneous expression in Sertoli cells, no expression in gonocytes, weak expression in nascent peritubular cells, and detectable GR in some prospermatogonia[137].

GR has also been detected in Leydig cells and germ cells of the testis[138,139] . Additionally, GR is present in the epithelial cells of the epididymis, seminal vesicles, vas deferens, and prostate gland[140,141].

Mineralocorticoid receptor

MR is expressed in the epithelial cells of the epididymis, with higher levels in the caput compared to the cauda[117], and in the testicular Leydig cells of adult rats, where aldosterone influences stem Leydig cell proliferation and testosterone production[142].

Endocrine disruptors and nuclear receptor signalling

Environmental pollutants that can mimic, inhibit, or block the synthesis of endogenous hormones or bind with their cognate receptors are classically known as endocrine-disrupting chemicals (EDCs). Reproduction in mammals largely depends on endocrine factors, and hence, any disturbances at this level could be detrimental to male fertility efficacy[13-18,143] . Some studies have shown that EDCs could modulate epigenetic signatures, thereby promoting even prostate cancer[25,144-146]. Here we present results pertaining to testicular toxicants and steroid hormone receptors in mammals, including human studies (**Fig 3**).

Bisphenols

Bisphenols are a group of chemicals structurally similar to bisphenol-A (BPA) which are used as the primary raw material in the production of polycarbonate and epoxy resins. Nowadays, there is major concern about the effect of bisphenol congeners on male reproductive health. In vitro studies indicated that bisphenol analogues bisphenol A (BPA), bisphenol F (BPF), bisphenol S (BPS), and brominated analogue flame retardant tetrabromobisphenol A (TBBPA) exhibit differential effects on steroidogenesis mediating human GR and AR in murine MA-10 Leydig cells[147]. The findings have shown that BPA, BPF, and TBBPA, but not BPS, showed

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GR and AR antagonism with IC50 values of 67 μM, 60 μM, and 22 nM for GR, and 39 μM, 20 μM, and 982 nM for AR, respectively. Interestingly, all bisphenol analogues and TBBPA altered testicular steroidogenesis wherein TBBPA was oriented towards induction of testosterone synthesis, while BPF and BPS were oriented towards progestagens which are formed at the initial steps of the steroidogenic pathway. In another study based on in vitro bioassays based on competitive binding assay, reporter gene expression, and cell proliferation assessment, the findings indicated that BPS, BPF, and BPA efficiently activated both human ERs, while TBBPA behaved as a weak hERα agonist and BPA, BPS were more active in the hERβ versus hERα assay[148]. With regards to hAR, BPF and BPA were full hAR antagonists, while BPS was a weak hAR agonist. The effect of bisphenol compounds could be pleiotropic in that they disrupt multiple steroid hormone receptors and may therefore interfere with the endocrine system[148]. Studies of Zhang et al. (2024) also indicated that BPA promotes cell proliferation and invasion ability of prostate cancer cells via regulating androgen receptor[25].

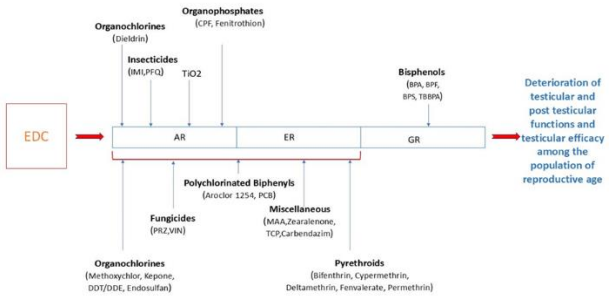

Figure 3: An illustration depicting the mechanism of action of endocrine disruptors induced deterioration of male reproductive health and fertility via mediating steroid hormone receptor. Dotted line: mechanism is not fully elucidated; -/+: down or up regulation of genes modulated by endocrine disruptors interfering with endogenous hormone mediated genomic actions; AR: Androgen receptor; GR: Glucocorticoid receptor; ER: Estrogen receptor

Pyrethroids

Pyrethroids like bifenthrin, cypermethrin, deltamethrin, fenvalerate, and permethrin are widely used to control pests. However, they exert adverse effects on male reproduction via their endocrine-disrupting properties[149,150]. These chemicals may act as antiandrogenic, estrogenic, and antiestrogenic in nature, thereby affecting hormone synthesis, metabolism, or transport of endogenous hormones. Studies by Wang et al. (2020) indicated that cypermethrin(CYP) can block AR and its co-regulators, such as SRC-1, SMRT, and NCoR, thereby causing improper transcriptional activation of downstream genes and interfering with the proper function of the male reproductive system[27]. Studies of Ding et al. (2020) reported that CYP can disrupt the interaction between AR and coactivators ARA70 and ARA55, leading to inhibition of AR signaling activation[151]. This novel aspect of toxicological mechanism contributes to the anti-androgenic activity of CYP and consequently is associated with male reproductive disorders[152,153].

Studies also indicated that bifenthrin, cypermethrin, deltamethrin, fenvalerate, and permethrin may exhibit estrogenic or antiestrogenic activity, thereby interfering with the ER pathway in males, suggesting that they may also interfere with the estrogen receptor (ER) pathway in males[154-157]. It is well known that disruption at the level of ER signaling can lead to decreased sperm count and impaired male fertility efficacy[158].

In contrast, a few studies also demonstrated that pyrethroids with either estrogenic or antiestrogenic effects may not affect male reproductive health[156,159], suggesting the type, dose, time point of exposure, animal model used, and most strikingly multifaceted effects of pyrethroids might be considered important in the assessment of their reproductive toxicity.

Organochlorines

Organochlorines such as methoxychlor, kepone, DDT/DDE, and endosulfan can mimic estrogens and are thus known as xenoestrogens. They interact with ERs and interfere with male reproduction[45]. The impact of endosulfan, an organochlorine pesticide, on estrogen-regulated genes. Endosulfan exposure modulated the expression of estrogen-dependent genes in a manner similar to a low, non-uterotrophic dose of 17β-estradiol. Although endosulfan did not induce uterine growth, a typical response to higher doses of estradiol, it influenced gene expression to mimic the hormone's effects at lower levels[160]. This suggests that endosulfan disrupts endocrine function by interacting with estrogen receptors, potentially leading to altered reproductive outcomes.

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Methoxychlor binds with low affinity to estrogen receptors α and β, disrupting normal development and function of male reproductive organs. This disruption affects steroidogenesis, leading to decreased testosterone levels, testicular atrophy, and impaired spermatogenesis. Methoxychlor's estrogenic activity also results in hormonal imbalances and oxidative stress, contributing to long-term reproductive toxicity, including delayed puberty and reduced fertility, sometimes passed to future generations through epigenetic mechanisms[161].

Dieldrin, was evaluated for its ability to interfere with endocrine function. The findings indicated that dieldrin significantly reduced the binding of [3H]5α-dihydrotestosterone (DHT) to the androgen receptor by around 30-40%.The mechanism underlying this effect involves dieldrin obstructing the normal interaction between steroid hormones and their receptors, particularly the androgen receptor. This disruption affects critical steroid hormone signaling pathways, which play a key role in regulating reproductive functions. By hindering the binding of natural hormones to their receptors, dieldrin may negatively affect androgen-dependent processes, potentially leading to reproductive issues. The study identified dieldrin as one of several environmental chemicals that can interfere with hormone-receptor binding, contributing to endocrine system disruption[162].

In the study by Pavlíková et al., the authors investigated the enantioselective effects of different isomers of alpha-hexachlorocyclohexane (HCH) on androgen receptor activity. Their research focused on how these isomers interact with androgen receptors in vitro.The study found that the various isomers of HCH exhibited different levels of activity in modulating androgen receptor function. Specifically, some isomers had a stronger effect on receptor activity than others. The researchers attributed these differences to the distinct molecular configurations of the HCH isomers, which influence their interaction with the androgen receptor. The findings suggest that the enantioselectivity of HCH isomers is a key factor in their endocrine-disrupting potential, impacting the androgen receptor's role in cellular processes[163].

Organophosphates

Organophosphates include pesticides such as chlorpyrifos (CPF) and fenitrothion. Studies on CPF indicated that exposure to males negatively affects fertility indicators like sperm quality and production and testosterone levels, and exhibits strong interactions with AR164. Molecular docking studies also indicated that CPF and its degradation products (chlorpyrifos-oxon [CPYO], desethyl chlorpyrifos [DEC], trichloromethoxypyridine [TMP], and trichloropyridinol [TCP]) showed potential interactions with AR. Therefore, CPF and its degradation products could be involved in the alteration of AR-LBD, thereby leading to dysfunction of the AR signaling[164].

Fenitrothion, an organophosphate insecticide, was act as an androgen receptor antagonist. By obstructing the normal binding of androgens like testosterone, fenitrothion impedes androgen receptor activation, disrupting male reproductive functions and secondary sexual characteristics[165].

Another significant finding comes from Erthal, which showed that malathion exposure during critical developmental stages led to significant downregulation of both androgen receptor and 17-β-HSD gene expression in rats, resulting in deteriorated sperm quality. This disruption in androgen receptor signaling, crucial for spermatogenesis and overall testicular function, highlights the reproductive toxicity of malathion during critical developmental periods[166].

Insecticides

Imidacloprid (IMI) is a neonicotinoid insecticide that targets the nervous system of insects. Studies have shown that IMI can interfere with the endocrine system in male animals[167,168]. The mechanism identified involves imidacloprid binding to the androgen receptor, which interferes with the receptor's normal function in regulating hormonal activity. This disruption impairs the androgen receptor's ability to properly bind testosterone, leading to disturbances in hormone signaling pathways. These alterations affect androgen-dependent processes, such as spermatogenesis and male reproductive development. The findings highlight that imidacloprid's interference with androgen receptor activity is a key factor in its endocrine-disrupting potential, potentially resulting in reproductive harm in male mice[169] Such disturbances affect processes reliant on androgens, including spermatogenesis and male reproductive development. The study emphasizes that imidacloprid's disruption of androgen receptor activity is a significant factor in its potential to disrupt the endocrine system, posing risks to male reproductive health in mice.

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Pyrifluquinazon (PFQ) is a commercialized insecticide that targets chordotonal receptor neuron function in insects. PFQ was shown to deteriorate testosterone levels, spermatogram properties associated with disruption of AR signaling pathway through altered testicular AR protein expression[170],. Interestingly, PFQ actions seem to be independent of ligand binding activity and could be ascribed to ligand-independent AR antagonist property of PFQ[170].

Fungicides

Prochloraz (PRZ) is an imidazole fungicide that is widely used to control fungus and protect agricultural crops. Studies have shown that PRZ can interact with ER and AR and also acts as an aromatase inhibitor, believed to suppress male reproductive tract functions via disruption of estrogen and androgen signaling on one hand and improper conversion of androgens to estrogens via inhibition of aromatase[171]. Vinclozolin (VIN) is a systemic dicarboximide fungicide used to protect various crops. Studies have shown that VIN and its metabolites, 2-[[(3,5-dichlorophenyl)-carboxymoyl]-2-methyl-3-butenoic acid (M1)] and 3′,5′-dichloro-2-hydroxy-2-methylbut-3-enanilide (M2), are potent antagonists of AR and moderate agonists to PR and ER[172]. Studies have shown that exposure of mice during the embryonic period, particularly during embryonic days 15.5-17.5, to EDCs like vinclozolin can pose a threat to penis development and could be associated with disruption of androgen signaling[173]. It has been shown that VIN acts as an antiandrogen and negatively affects penis development and overall masculinization in mice[173].

olychlorinated Biphenyls (PCBs)

Polychlorinated biphenyls (PCB) are used as additives in paints, plastics, printing inks, copying paper, and sealants and also used as a fluid in electrical transformers and capacitors, lubricating and cutting oils, hydraulic fluids, and heat transfer fluids. Studies have shown that Aroclor 1254 is a commercial PCB and its exposure caused reduced AR expression, indicating defective expression of the AR gene[174]. Studies of Selvakumar et al.,(2011) reported that rats exposed to PCBs showed downregulation of AR and ERalpha mRNA and protein levels in the ventral prostate, while ERbeta mRNA and its protein expression were increased due to low availability of estrogens and testosterone[175].

Miscellaneous Chemicals

Methoxyacetic acid (MAA) is a widely used industrial solvent and is a metabolite of ethylene glycol ether 2-methoxyethanol (ME). MAA acts as a hormone sensitizer and enhances the NR-mediated transactivations without itself being a hormone mimic[176]. Male reproductive toxicity of MAA has been studied in rodent models[177]. Studies have shown that exposure of experimental rats to MAA causes increased prevalence of oligospermia and azoospermia, deterioration of sperm quality, and most strikingly apoptosis in pachytene spermatocytes[178]. Apoptosis of primary spermatocytes and testicular degradation associated with normal testosterone levels but can be indicative of androgen deprivation following MAA treatment. Based on their findings, they postulated that MAA-induced testicular toxicity, at least in part, mediates altered AR signaling leading to a change in the balance between androgenic and estrogenic activity, which is a prerequisite of normal testicular development[179]. Moreover, MAA can target several genes in the testes that are regulated by AR signaling pathways[180].

Titanium Dioxide Fine Particles (TiO2FPs)

Recent examination of titanium dioxide fine particles (TiO2FPs) on male reproduction indicated that the oral administration of TiO2 FPs resulted in developmental toxicity at the level of reproductive organs like atrophy of the seminal vesicles[181]. Further, these authors also demonstrated that the mechanism of TiO2 action on the male reproductive system could be ascribed to its antiandrogenic property by suppressing AR expression, as evidenced by immunohistochemical examination and gene expression analysis. Due to blocking AR sites, the adequate supply of androgens to the seminal vesicles was blocked, which eventually caused developmental abnormalities[181].

Other Chemicals

Zearalenone is a mycotoxin that acts primarily as an estrogenic disruptor by mimicking estrogen and binding to estrogen receptors. This mimicry affects sperm production, hormone levels, and reproductive organ function. Additionally, zearalenone's non-estrogenic effects, including influencing oxidative stress and inflammatory responses, further impair reproductive health[182]. 5,6-trichloro-2-pyridinol (TCP) was found to exacerbate the impact of chlorpyrifos by interfering with testosterone binding to the androgen receptor. This disruption impairs Sertoli cell functions, leading to

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altered spermatogenesis and potential reproductive issues[183]. Low doses of carbendazim lead to significant disruptions in sperm production. The fungicide affects spermatogenesis through mechanisms involving estrogen receptors, altering epigenetic modifications crucial for gene regulation[184].

Conclusion

To summate, it is fact that the current knowledge of the steroid hormone receptors has drastically expanded within the last decade due to advancements in both analytical and genome-wide methodologies led to the identification of new co-regulator proteins that modulate receptor activity and new signalling pathways. Moreover, as steroid hormone receptors upon binding to their ligands control the expression of diverse array of genes. Indeed, as hormones do not act in isolation but instead exhibit pleiotropic effects and hence, their crosstalk and interactions are of paramount importance. For example, the high affinity of progesterone for the MR which antagonizes activation of the MR by aldosterone in humans, rats, alligators and frogs[185]. On the other hand, EDCs are not explicitly specific for one receptor but instead their crosstalk with target NRs tend to have unwanted side effects on male reproduction[186]. Finally, given that humans are exposed to hundreds of chemicals, there is a need for screening tools that can aid in the risk assessment of potential EDCs. This notion needs to be carefully monitored in order to understand the mechanisms that guide NR regulation. Therefore, a systems biology approach integrating these multifactorial interactions is a key to understand the possible NR signalling mechanisms underlying EDCs on male reproductive health and the knowledge gained could be used to develop future therapeutics and might be helpful to protect male fertility efficacy among the population at reproductive age.

References

1. World Health Organization (WHO). 2020. Infertility.
2. Levine H., Jørgensen N., Martino-Andrade A., Mendiola J., Weksler-Derri D., Mindlis I., Pinotti R., Swan S.H., 2017. Temporal trends in sperm count: A systematic review and meta-regression analysis. *Hum Reprod Update*. 23(6): 646–659.
3. Boisen K.A., Kaleva M., Main K.M., Virtanen H.E., Haavisto A.-M., Schmidt I.M., Chellakooty M., Damgaard I.N., Mau C., Reunanen M., Skakkebaek N.E., Toppari J., 2004. Difference in prevalence of congenital cryptorchidism in infants between two Nordic countries. *The Lancet*. 363(9417): 1264–1269.
4. Skakkebaek N.E., Rajpert-De Meyts E., Main K.M., Vom Saal F., Skakkeboek N., Joffe M., Sharpe R., Swan S.H., Guillette L., Iwamoto T., 2001. Testicular dysgenesis syndrome: An increasingly common developmental disorder with environmental aspects. *APMIS*. 109(103): S22–S30.
5. Skakkebaek N.E., Rajpert-De Meyts E., Buck Louis G.M., Toppari J., Andersson A.M., Eisenberg M.L., Jensen T.K., Jørgensen N., Swan S.H., Sapra K.J., Ziebe S., Priskorn L., Juul A., 2016. Male reproductive disorders and fertility trends: Influences of environment and genetic susceptibility. *Physiol Rev*. 96(1): 55–97.
6. Thankamony A., Pasterski V., Ong K.K., Acerini C.L., Hughes I.A., 2016. Anogenital distance as a marker of androgen exposure in humans. *Andrology*. 4(4): 616–625.
7. Fisher H.S., Jacobs-Palmer E., Lassance J.-M., Hoekstra H.E., 2016. The genetic basis and fitness consequences of sperm midpiece size in deer mice. *Nat Commun*. 7: Article 13060.
8. Virtanen H.E., Jørgensen N., Toppari J., 2017. Semen quality in the 21st century. *Nat Rev Urol*. 14: 120–130.
9. Virtanen H.E., Main K.M., Toppari J., 2019. Association of endocrine disrupting chemicals with male reproductive health. In: Huhtaniemi I., editor. *Encyclopedia of Endocrine Diseases*. 2nd ed. Oxford: Academic Press; p. 802–811.
10. Gurney J.K., McGlynn K.A., Stanley J., Merriman T., Signal V., Shaw C., Edwards R., Richiardi L., Hutson J., Sarfati D., 2017. Risk factors for cryptorchidism. *Nat Rev Urol*. 14: 534–548.
11. Lind D.V., Main K.M., Kyhl H.B., Kristensen D.M., Toppari J., Andersen H.R., Andersen M.S., Skakkebæk N.E., Jensen T.K., 2017. Maternal use of mild analgesics during pregnancy associated with reduced anogenital distance in sons: A cohort study of 1027 mother-child pairs. *Hum Reprod*. 32: 223–231.
12. Sifakis S., Androutsopoulos V.P., Tsatsakis A.M., Spandidos D.A., 2017. Human exposure to

endocrine disrupting chemicals: Effects on the male and female reproductive systems. *Environ Toxicol Pharmacol*. 51: 56–70.

13. Radke E.G., Braun J.M., Meeker J.D., Cooper G.S., 2018. Phthalate exposure and male reproductive outcomes: A systematic review of the human epidemiological evidence. *Environ Int*. 121: 764–793.

14. Arbuckle T.E., Agarwal A., MacPherson S.H., Fraser W.D., Sathyanarayana S., Ramsay T., Dodds L., Muckle G., Fisher M., Foster W., Walker M., Monnier P., 2018. Prenatal exposure to phthalates and phenols and infant endocrine-sensitive outcomes: The MIREC study. *Environ Int*. 120: 572–583.

15. Mammadov E., Uncu M., Dalkan C., 2018. High prenatal exposure to bisphenol A reduces anogenital distance in healthy male newborns. *J Clin Res Pediatr Endocrinol*. 10: 25–29.

16. Haraux E., Tourneux P., Kouakam C., Stephan-Blanchard E., Boudailliez B., Leke A., et al., 2018. Isolated hypospadias: The impact of prenatal exposure to pesticides, as determined by meconium analysis. *Environ Int*. 119: 20–25.

17. Warembourg C., Botton J., Lelong N., Rouget F., Khoshnood B., Le Gléau F., et al., 2018. Prenatal exposure to glycol ethers and cryptorchidism and hypospadias: A nested case-control study. *Occup Environ Med*. 75(1): 59–65.

18. Schwartz C.L., Christiansen S., Vinggaard A.M., Axelstad M., Hass U., Svingen T., 2019. Anogenital distance as a toxicological or clinical marker for fetal androgen action and risk for reproductive disorders. *Arch Toxicol*. 93: 253–272.

19. Rodprasert W., Main K.M., Toppari J., Virtanen H.E., 2019. Associations between male reproductive health and exposure to endocrine-disrupting chemicals. *Curr Opin Endocr Metab Res*. 7: 49–61.

20. Li Y., Li R.-H., Ran M.-X., Zhang Y., Liang K., Ren Y.-N., 2018. High-throughput small RNA and transcriptome sequencing reveal capacitation-related microRNAs and mRNA in boar sperm. *BMC Genomics*. 19: 736.

21. Viberg H., Athanasiadou M., Athanassiadis I., Fent K., 2010. Effects of endocrine disrupting chemicals (EDCs) on wildlife, with special emphasis on the European situation. *Environ Int*. 36(5): 369–382.

22. Walker W.H., Cooke P.S., 2023. Functions of steroid hormones in the male reproductive tract as revealed by mouse models. *Int J Mol Sci*. 24(3): Article 2748.

23. Cariati F., Carbone L., Conforti A., Bagnulo F., Peluso S.R., Carotenuto C., Buonfantino C., Alviggi E., Alviggi C., 2020. Bisphenol A-induced epigenetic changes and its effects on the male reproductive system. *Front Endocrinol*. 11: Article 453.

24. Hlisníková H., Petrovičová I., Kolena B., Šidlovská M., Sirotkin A., 2020. Effects and mechanisms of phthalates' action on reproductive processes and reproductive health: A literature review. *Int J Environ Res Public Health*. 17(18): 6811.

25. Zhang Y., Xie J., Ouyang Y., Li S., Sun Y., Tan W., Ren L., Zhou X., 2024. Adverse outcome pathways of PBDEs inducing male reproductive toxicity. *Environ Res*. 240(Part 1): Article 117598.

26. Jayaraj R., Megha P., Sreedev P., 2016. Organochlorine pesticides, their toxic effects on living organisms and their fate in the environment. *Interdiscip Toxicol*. 9(3–4): 90–100.

27. Wang Q., Shen J.Y., Zhang R., Hong J.W., Li Z., Ding Z., Wang H.X., Zhang J.P., Zhang M.R., Xu L.C., 2020. Effects and mechanisms of pyrethroids on the male reproductive system. *Toxicology*. 438: Article 152460.

28. Moreira S., Silva R., Carrageta D.F., Alves M.G., Seco-Rovira V., Oliveira P.F., Pereira M.D.L., 2022. Carbamate pesticides: Shedding light on their impact on the male reproductive system. *Int J Mol Sci*. 23(15): Article 8206.

29. Hamed M.A., Akhigbe T.M., Adeogun A.E., Adesoye O.B., Akhigbe R.E., 2023. Impact of organophosphate pesticides exposure on human semen parameters and testosterone: A systematic review and meta-analysis. *Front Endocrinol*. 14: Article 14.

30. Giska I., Babik W., van Gestel C.A., van Straalen N.M., Laskowski R., 2015. Genome-wide genetic diversity of rove beetle populations along a metal pollution gradient. *Ecotoxicol Environ Saf.* 119: 98–105.

31. Cho S., Yoon J.Y., 2017. Organ-on-a-chip for assessing environmental toxicants. *Curr Opin Biotechnol.* 45: 34–42.

32. Tiwana M.S., Leslie S.W., 2022. Anatomy, Abdomen and Pelvis, Testicle. *StatPearls* [Internet]. StatPearls Publishing; Treasure Island (FL): Jul 25, 2022.

33. Oduwole O.O., Peltoketo H., Poliandri A., Vengadabady L., Chrusciel M., Doroszko M., et al., 2018. Constitutively active follicle-stimulating hormone receptor enables androgen-independent spermatogenesis. *J Clin Invest.* 128: 1787–1792.

34. Sriraman V., Anbalagan M., Rao A.J., 2005. Hormonal regulation of Leydig cell proliferation and differentiation in rodent testis: A dynamic interplay between gonadotrophins and testicular factors. *Reprod Biomed Online.* 11(4): 507–518.

35. Walker W.H., Cheng J., 2005. FSH and testosterone signaling in Sertoli cells. *Reproduction.* 130(1): 15–28.

36. Ruwanpura S.M., McLachlan R.I., Meachem S.J., 2010. Hormonal regulation of male germ cell development. *J Endocrinol.* 205: 117–131.

37. Hayes F.J., DeCruz S., Seminara S.B., Boepple P.A., Crowley W.F. Jr., 2001. Differential regulation of gonadotropin secretion by testosterone in the human male: Absence of a negative feedback effect of testosterone on follicle-stimulating hormone secretion. *J Clin Endocrinol Metab.* 86(1): 53–58.

38. Zheng J., Mao J., Cui M., Liu Z., Wang X., Xiong S., et al., 2017. Novel FSHβ mutation in a male patient with isolated FSH deficiency and infertility. *Eur J Med Genet.* 60: 335–339.

39. Oduwole O.O., Huhtaniemi I.T., Misrahi M., 2021. The roles of luteinizing hormone, follicle-stimulating hormone, and testosterone in spermatogenesis and folliculogenesis revisited. *Int J Mol Sci.* 22(23): 12735.

40. Behre H.M., 2019. Clinical use of FSH in male infertility. *Front Endocrinol.* 10: 322.

41. Kazmi S.R.H., Can A.S., 2023. Luteinizing hormone deficiency. In: *StatPearls* [Internet]. StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562266/ .

42. Schiffer L., Arlt W., Storbeck K.H., 2018. Intracrine androgen biosynthesis, metabolism and action revisited. *Mol Cell Endocrinol.* 465: 4–26.

43. Rahmani A.H., Alzohairy M., Babiker A.Y.Y., Khan A.A., Aly S.M., Rizvi M.A., 2013. Implication of androgen receptor in urinary bladder cancer: A critical mini-review. *Int J Mol Epidemiol Genet.* 4(3): 150–155.

44. Guercio G., Saraco N., Costanzo M., Marino R., Ramirez P., Berensztein E., Rivarola M.A., Belgorosky A., 2020. Estrogens in human male gonadotropin secretion and testicular physiology from infancy to late puberty. *Front Endocrinol (Lausanne).* 11: 72.

45. Cooke P.S., Nanjappa M.K., Ko C., Prins G.S., Hess R.A., 2017. Estrogens in male physiology. *Physiol Rev.* 97(3): 995–1043.

46. Sheikh I.A., Beg M.A., Abo-Almagd T., Hamoda A.M., Mandourah H.M.S., Memili E., 2023. Androgen receptor signaling and pyrethroids: Potential male infertility consequences. *Front Cell Dev Biol.* 11.

47. Bhimsaria D., Rodríguez-Martínez J.A., Mendez-Johnson J.L., Ghoshdastidar D., Varadarajan A., Bansal M., Daniels D.L., Ramanathan P., Ansari A.Z., 2023. Hidden modes of DNA binding by human nuclear receptors. *Nat Commun.* 14: 4179.

48. Evans R.M., Mangelsdorf D.J., 2014. Nuclear receptors, RXR, and the big bang. *Cell.* 157(1): 255–266.

49. Lazar M.A., 2017. Maturing of the nuclear receptor family. *J Clin Invest.* 127(4): 1123–1125.

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www.jchr.org

JCHR (2026) 16(2), 3036-3057 | ISSN:2251-6727

50. Bommer M., Benecke A., Gronemeyer H., Rochette-Egly C., 2002. TIF2 mediates the synergy between RARalpha 1 activation functions AF-1 and AF-2. *J Biol Chem.* 277: 37961–37966.

51. Gianni M., Tarrade A., Nigro E.A., Garattini E., Rochette-Egly C., 2003. The AF-1 and AF-2 domains of RAR gamma 2 and RXR alpha cooperate for triggering the transactivation and the degradation of RAR gamma 2/RXR alpha heterodimers. *J Biol Chem.* 278: 34458–34466.

52. Bugge A., Grøntved L., Aagaard M.M., Borup R., Mandrup S., 2009. The PPARγ2 A/B-domain plays a gene-specific role in transactivation and cofactor recruitment. *Mol Endocrinol.* 23: 794–808.

53. Askew E.B., Minges J.T., Hnat A.T., Wilson E.M., 2012. Structural features discriminate androgen receptor N/C terminal and coactivator interactions. *Mol Cell Endocrinol.* 348: 403–410.

54. Hill K.K., Roemer S.C., Churchill M.E., Edwards D.P., 2012. Structural and functional analysis of domains of the progesterone receptor. *Mol Cell Endocrinol.* 348: 418–429.

55. Zhou D., Quach K.M., Yang C., Lee S.Y., Pohajdak B., Chen S., 2000. PNRC: A proline-rich nuclear receptor coregulatory protein that modulates transcriptional activation of multiple nuclear receptors including orphan receptors SF1 (Steroidogenic Factor 1) and ERRα1 (Estrogen Related Receptor α-1). *Mol Endocrinol.* 14(7): 986–992.

56. Umesono K., Evans R.M., 1989. Determinants of target gene specificity for steroid/thyroid hormone receptors. *Cell.* 57: 1139–1146.

57. Tan M.H., Li J., Xu H.E., Melcher K., Yong E.L., 2015. Androgen receptor: Structure, role in prostate cancer, and drug discovery. *Acta Pharmacol Sin.* 36: 3–23.

58. Mangelsdorf D.J., Thummel C., Beato M., Herrlich P., Schütz G., Umesono K., Blumberg B., Kastner P., Mark M., Chambon P., et al., 1995. The nuclear receptor superfamily: The second decade. *Cell.* 83: 835–839.

59. Claessens F., Gewirth D.T., 2004. DNA recognition by nuclear receptors. *Essays Biochem.* 40: 59–72.

60. Pawlak M., Lefebvre P., Staels B., 2012. General molecular biology and architecture of nuclear receptors. *Curr Top Med Chem.* 12: 486–504.

61. Anbalagan M., Huderson B., Murphy L., Rowan B.G., 2012. Post-translational modifications of nuclear receptors and human disease. *Nucl Recept Signal.* 10: e001.

62. Huang P., Chandra V., Rastinejad F., 2010. Structural overview of the nuclear receptor superfamily: Insights into physiology and therapeutics. *Annu Rev Physiol.* 72: 247–272.

63. Simons S.S. Jr., Edwards D.P., Kumar R., 2014. Minireview: Dynamic structures of nuclear hormone receptors: New promises and challenges. *Mol Endocrinol.* 28: 173–182.

64. Cathcart P., Lucchesi W., Ottaviani S., De Giorgio A., Krell J., 2015. Noncoding RNAs and the control of signalling via nuclear receptor regulation in health and disease. *Best Pract Res Clin Endocrinol Metab.* 29(4): 529–543.

65. Hall J.M., McDonnell D.P., Korach K.S., 2002. Allosteric regulation of estrogen receptor structure, function, and coactivator recruitment by different estrogen response elements. *Mol Endocrinol.* 16: 469–486.

66. Chang C., Saltzman A., Yeh S., Young W., Keller E., Lee H.J., et al., 1995. Androgen receptor: an overview. *Crit Rev Eukaryot Gene Expr.* 5: 97–125.

67. Davey R.A., Grossmann M., 2016. Androgen receptor structure, function and biology: From bench to bedside. *Clin Biochem Rev.* 37(1): 3–15.

68. Rana K., Davey R.A., Zajac J.D., 2014. Human androgen deficiency: Insights gained from androgen receptor knockout mouse models. *Asian J Androl.* 16: 169–177.

69. Cooke P.S., Young P., Cunha G.R., 1991. Androgen receptor expression in developing male reproductive organs. *Endocrinology.* 128: 2867–2873.

70. Chang C., Lee S.O., Wang R-S., Yeh S., Chang T-M., 2013. Androgen receptor (AR) physiological roles in male and female reproductive systems: Lessons learned from AR-knockout mice lacking AR in selective cells. *Biol Reprod.* 89(1): 21.

71. Gelmann E.P., 2002. Molecular biology of the androgen receptor. *J Clin Oncol.* 20: 3001–3015.

72. MacLean H.E., Chu S., Warne G.L., Zajac J.D., 1993. Related individuals with different androgen receptor gene deletions. *J Clin Invest.* 91: 1123–1128.

73. De Gendt K., Atanassova N., Tan K.A., de Franca L.R., Parreira G.G., McKinnell C., Sharpe R.M., Saunders P.T., Mason J.I., Hartung S., Ivell R., Denolet E., Verhoeven G., 2005. Development and function of the adult generation of Leydig cells in mice with Sertoli cell-selective or total ablation of the androgen receptor. *Endocrinology.* 146(9): 4117–4126.

74. Berthrong M., Goodwin W.E., Scott W.W., 1949. Estrogen production by the testis. *J Clin Endocrinol Metab.* 9(7): 579–592.

75. Carmeci C., Thompson D.A., Ring H.Z., Francke U., Weigel R.J., 1997. Identification of a gene (GPR30) with homology to the G-protein-coupled receptor superfamily associated with estrogen receptor expression in breast cancer. *Genomics.* 45: 607–615.

76. Pelletier G., El-Alfy M., 2000. Immunocytochemical localization of estrogen receptors alpha and beta in the human reproductive organs. *J Clin Endocrinol Metab.* 85: 4835–4840.

77. Carreau S., Bouraima-Lelong H., Delalande C., 2012. Role of estrogens in spermatogenesis. *Front Biosci (Elite Ed).* 4: 1–11.

78. Cavaco J.E., Laurentino S.S., Barros A., Sousa M., Socorro S., 2009. Estrogen receptors alpha and beta in human testis: both isoforms are expressed. *Syst Biol Reprod Med.* 55: 137–144.

79. Boukari K., Ciampi M.L., Guiochon-Mantel A., Young J., Lombes M., Meduri G., 2007. Human fetal testis: source of estrogen and target of estrogen action. *Hum Reprod.* 22: 1885–1892.

80. Zaya R., Hennick C., Pearl C.A., 2012. In vitro expression of androgen and estrogen receptors in prepubertal and adult rat epididymis. *Gen Comp Endocrinol.* 178(3): 573–586.

81. Kolasa A., Wiszniewska B., Marchlewicz M., Wenda-Rozewicka L., 2003. Localisation of oestrogen receptors (ERalpha and ERbeta) in the human and rat epididymides. *Folia Morphol.* 62: 467–469.

82. Aquila S., Sisci D., Gentile M., Middea E., Catalano S., Carpino A., Rago V., Ando S., 2004. Estrogen receptor (ER)alpha and ER beta are both expressed in human ejaculated spermatozoa: evidence of their direct interaction with phosphatidylinositol-3-OH kinase/Akt pathway. *J Clin Endocrinol Metab.* 89: 1443–1451.

83. Fisher J.S., Millar M.R., Majdic G., Saunders P.T., Fraser H.M., Sharpe R.M., 1997. Immunolocalisation of oestrogen receptor-alpha within the testis and excurrent ducts of the rat and marmoset monkey from perinatal life to adulthood. *J Endocrinol.* 153: 485–495.

84. O'Donnell L., Robertson K.M., Jones M.E., Simpson E.R., 2001. Estrogen and spermatogenesis. *Endocr Rev.* 22: 289–318.

85. Hess R.A., Fernandes S.A., Gomes G.R., Oliveira C.A., Lazari M.F., Porto C.S., 2011. Estrogen and its receptors in efferent ductules and epididymis. *J Androl.* 32: 600–613.

86. Rossouw J.E., Anderson G.L., Prentice R.L., LaCroix A.Z., Kooperberg C., Stefanick M.L., Jackson R.D., Beresford S.A., Howard B.V., Johnson K.C., Kotchen J.M., 2002. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 288: 321–333.

87. Dahlman-Wright K., Cavailles V., Fuqua S.A., Jordan V.C., Katzenellenbogen J.A., Korach K.S., Maggi A., Muramatsu M., Parker M.G., Gustafsson JÅ, 2006. International Union of Pharmacology. LXIV. Estrogen Receptors. *Pharmacol Rev.* 58: 773–781.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(2), 3036-3057 | ISSN:2251-6727

88. Ponglikitmongkol M., Green S., Chambon P., 1988. Genomic organization of the human oestrogen receptor gene. *EMBO J.* 7: 3385–3388.

89. Ogawa S., Inoue S., Watanabe T., et al., 1998. The complete primary structure of human estrogen receptor beta (hER beta) and its heterodimerization with ER alpha in vivo and in vitro. *Biochem Biophys Res Commun.* 243: 122–126.

90. Sand P., Luckhaus C., Schlurmann K., Götz M., Deckert J., 2002. Untangling the human estrogen receptor gene structure. *J Neural Transm.* 109: 567–583.

91. Kuiper G.G., Enmark E., Pelto-Huikko M., Nilsson S., Gustafsson J.A., 1996. Cloning of a novel estrogen receptor expressed in rat prostate and ovary. *Proc Natl Acad Sci USA.* 93(12): 5925–5930.

92. Mosselman S., Polman J., Dijkema R., 1996. ER beta: identification and characterization of a novel human estrogen receptor. *FEBS Lett.* 392(1): 49–53.

93. Tremblay G.B., Tremblay A., Copeland N.G., et al., 1997. Cloning, chromosomal localization, and functional analysis of the murine estrogen receptor beta. *Mol Endocrinol.* 11(3): 353–365.

94. Cowley S.M., Hoare S., Mosselman S., Parker M.G., 1997. Estrogen receptors alpha and beta form heterodimers on DNA. *J Biol Chem.* 272(32): 19858–19862.

95. Clarke C.L., Sutherland R.L., 1990. Progestin regulation of cellular proliferation. *Endocrine Rev.* 11: 266–300.

96. Lydon J.P., DeMayo F.J., Funk C.R., et al., 1995. Mice lacking progesterone receptor exhibit pleiotropic reproductive abnormalities. *Genes Dev.* 9: 2266–2278.

97. Asavasupreechar T., Saito R., Miki Y., Edwards D.P., Boonyaratanakornkit V., Sasano H., 2020. Systemic distribution of progesterone receptor subtypes in human tissues. *J Steroid Biochem Mol Biol.* 199: 105599.

98. Nieuwenhuizen A.G., Schuiling G.A., Liem S.M., Moes H., Koiter T.R., Uilenbroek J.T., 1999. Progesterone stimulates pancreatic cell proliferation in vivo. *Eur J Endocrinol.* 140(3): 256–263.

99. Wang F., Zheng T.Z., Li W., Qu S.Y., He D.Y., 2003. Action of progesterone on contractile activity of isolated gastric strips in rats. *World J Gastroenterol.* 9(4): 775–778.

100. Schulz K.M., Sisk C.L., 2016. The organizing actions of adolescent gonadal steroid hormones on brain and behavioral development. *Neurosci Biobehav Rev.* 70: 148–158.

101. Vigil P., Del Río J.P., Carrera B., Aránguiz F.C., Rioseco H., Cortés M.E., 2016. Influence of sex steroid hormones on the adolescent brain and behavior: an update. *Linacre Q.* 83(3): 308–329.

102. Kastner P., Mark M., Chambon P., et al., 1995. The nuclear receptor superfamily: The second decade. *Cell.* 83: 835–839.

103. Sartorius C.A., Melville M.Y., Hovland A.R., Tung L., Takimoto G.S., Horwitz K.B., 1994. A third transactivation function (AF3) of human progesterone receptors located in the unique N-terminal segment of the B isoform. *Mol Endocrinol.* 8: 1347–1360.

104. Takimoto G.S., Tung L., Abdel-Hafiz H., Abel M.G., Sartorius C.A., Richer J.K., Jacobsen B.M., Bain D.L., Horwitz K.B., 2003. Functional properties of the N-terminal region of progesterone receptors and their mechanistic relationship to structure. *J Steroid Biochem Mol Biol.* 85: 209–219.

105. Tung L., Mohamed M.K., Hoeffler J.P., Takimoto G.S., Horwitz K.B., 1993. Antagonist-occupied human progesterone B-receptors activate transcription without binding to progesterone response elements and are dominantly inhibited by A-receptors. *Mol Endocrinol.* 7: 1256–1265.

106. Beato M., Klug J., 2000. Steroid hormone receptors: An update. *Hum Reprod Update.* 6: 225–236.

107. Boumpas D.T., Chrousos G.P., Wilder R.L., Cupps T.R., Balow J.E., 1993. Glucocorticoid therapy for immune-mediated diseases: basic and clinical correlates. *Ann Intern Med.* 119: 1198–1208.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(2), 3036-3057 | ISSN:2251-6727

108. Schmid W., Cole T.J., Blendy J.A., Schütz G., 1995. Molecular genetic analysis of glucocorticoid signaling in development. *J Steroid Biochem Mol Biol.* 53: 33–35.

109. Silva E.J., 2014. Impact of adrenalectomy and dexamethasone treatment on testicular morphology and sperm parameters in rats: Insights into the adrenal control of male reproduction. *Andrology.* 2: 835–846.

110. Whitfield G.K., Jurutka P.W., Haussler C.A., Haussler M.R., 1999. Steroid hormone receptors: evolution, ligands, and molecular basis of biologic function. *J Cell Biochem.* suppl 32–33: 110–122.

111. Androutsellis-Theotokis A., Chrousos G.P., McKay R.D., DeCherney A.H., Kino T., 2013. Expression profiles of the nuclear receptors and their transcriptional coregulators during differentiation of neural stem cells. *Horm Metab Res.* 45: 159–168.

112. Oakley R.H., Sar M., Cidlowski J.A., 1996. The human glucocorticoid receptor β isoform: expression, biochemical properties, and putative function. *J Biol Chem.* 271: 9550–9559.

113. Vandevyver S., Dejager L., Libert C., 2012. On the trail of the glucocorticoid receptor: into the nucleus and back. *Traffic.* 13: 364–374.

114. Kino T., Gragerov A., Kopp J.B., Stauber R.H., Pavlakis G.N., Chrousos G.P., 1999. The HIV-1 virion-associated protein vpr is a coactivator of the human glucocorticoid receptor. *J Exp Med.* 189: 51–62.

115. Funder J.W., 2005. Mineralocorticoid receptors: distribution and activation. *Heart Fail Rev.* 10: 15–22.

116. Kishimoto T., Fukawa T., Yamaguchi K., Yamamoto Y., Nakatsuji H., Izaki H., Kanayama H., 2013. Mineralocorticoid receptor expression in human penile corpus cavernosum. *J Med Investig.* 60(1.2): 21–26.

117. Waddell B.J., Hisheh S., Krozowski Z.S., Burton P.J., 2003. Localization of 11β-Hydroxysteroid Dehydrogenase Types 1 and 2 in the Male Reproductive Tract. *Endocrinology.* 144(7): 3101–3106.

118. Reul J.M., de Kloet E.R., 1985. Two receptor systems for corticosterone in rat brain: microdistribution and differential occupation. *Endocrinology.* 117: 2505–2511.

119. Pratt D.O., Toft D., 1997. Steroid receptor interactions with heat shock protein and immunophilin chaperones. *Endocr Rev.* 18(3): 306–360.

120. Matsuyama S., DeFalco T., 2024. Steroid hormone signaling: multifaceted support of testicular function. *Front Cell Dev Biol.* 11: 1339385.

121. De Gendt K., Swinnen J.V., Saunders P.T., Schoonjans L., Dewerchin M., Devos A., et al., 2004. A Sertoli cell-selective knockout of the androgen receptor causes spermatogenic arrest in meiosis. *Proc Natl Acad Sci U S A.* 101(5): 1327–1332.

122. Edelsztein N.Y., Racine C., di Clemente N., Schteingart H.F., Rey R.A., 2018. Androgens downregulate anti-Müllerian hormone promoter activity in the Sertoli cell through the androgen receptor and intact steroidogenic factor 1 sites. *Biol Reprod.* 99(6): 1303–1312.

123. Takada M., Fukuhara D., Takiura T., Nishibori Y., Kotani M., Kiuchi Z., et al., 2023. Involvement of GLCCI1 in mouse spermatogenesis. *FASEB J.* 37(1): e22680.

124. Smith L.B., Walker W.H., 2014. The regulation of spermatogenesis by androgens. *Semin Cell Dev Biol.* 30: 2–13.

125. Shang Y., Myers M., Brown M., 2002. Formation of the androgen receptor transcription complex. *Mol Cell.* 9(3): 601–610.

126. Benten W.P., Lieberherr M., Giese G., Wrehlke C., Stamm O., Sekeris C.E., et al., 1999. Functional testosterone receptors in plasma membranes of T cells. *FASEB J.* 13(1): 123–133.

127. Valeri C., Lovaisa M.M., Racine C.Y., Edelsztein N.Y., Riggio M., Giulianelli S., et al., 2020. Molecular mechanisms underlying AMH elevation

in hyperoestrogenic states in males. *Sci Rep.* 10(1): 15062.

128. Jefferson W.N., Couse J.F., Banks E.P., Korach K.S., Newbold R.R., 2000. Expression of estrogen receptor beta is developmentally regulated in reproductive tissues of male and female mice. *Biol Reprod.* 62(2): 310–317.

129. Lue Y., Wang C., Lydon J.P., Leung A., Li J., Swerdloff R.S., 2013. Functional role of progestin and the progesterone receptor in the suppression of spermatogenesis in rodents. *Andrology.* 1(2): 308–317.

130. Shah C., Modi D., Sachdeva G., Gadkar S., Puri C., 2005. Coexistence of intracellular and membrane-bound progesterone receptors in human testis. *J Clin Endocrinol Metab.* 90(1): 474–483.

131. Luetjens C.M., Didolkar A., Kliesch S., Paulus W., Jeibmann A., Böcker W., et al., 2006. Tissue expression of the nuclear progesterone receptor in male non-human primates and men. *J Endocrinol.* 189(3): 529–539.

132. Rossato M., Nogara A., Merico M., Ferlin A., Foresta C., 1999. Identification of functional binding sites for progesterone in rat Leydig cell plasma membrane. *Steroids.* 64: 168–75.

133. Tesarik J., Mendonza C., Moos J., Carreras A., 1992. Selective expression of progesterone receptor on sperm surface. *Fertil Steril.* 58: 784–92.

134. Hazra R., Upton D., Jimenez M., Desai R., Handelsman D.J., Allan C.M., 2014. In vivo actions of the Sertoli cell glucocorticoid receptor. *Endocrinology.* 155(3): 1120–1130.

135. Levy F.O., Ree A.H., Eikvar L.H., Govindan M.V., Jahnsen T., Hansson V., 1989. Glucocorticoid receptors and glucocorticoid effects in rat Sertoli cells. *Endocrinology.* 124(1): 430–436.

136. Welter H., Herrmann C., Dellweg N., Missel A., Thanisch C., Urbanski H.F., et al., 2020. The glucocorticoid receptor NR3C1 in testicular peritubular cells is developmentally regulated and linked to the smooth muscle-like cellular phenotype. *J Clin Med.* 9(4): 961.

137. Nordkap L., Almstrup K., Nielsen J.E., Bang A.K., Priskorn L., Krause M., et al., 2017. Possible involvement of the glucocorticoid receptor (NR3C1) and selected NR3C1 gene variants in regulation of human testicular function. *Andrology.* 5(6): 1105–14.

138. Dondi D., Maggi R., Scaccianoce E., Martini L., Motta M., Poletti A., 2001. Expression and role of functional glucocorticoid receptors in the human androgen-independent prostate cancer cell line, DU145. *J. Mol. Endocrinol.* 26: 185–191.

139. Biagini G., Pich E.M., 2002. Corticosterone administration to rat pups, but not maternal separation, affects sexual maturation and glucocorticoid receptor immunoreactivity in the testis. *Pharmacol Biochem Behav.* 73: 95–103.

140. Silva E.J.R., Queiróz D.B.C., Honda L., Avellar M.C.W., 2010. Glucocorticoid receptor in the rat epididymis: Expression, cellular distribution, and regulation by steroid hormones. *Mol Cell Endocrinol.* 325(1-2): 64–77.

141. Schultz R., Isola J., Parvinen M., Honkaniemi J., Wikström A.C., Gustafsson J.A., Pelto-Huikko M., 1993. Localization of the glucocorticoid receptor in testis and accessory sexual organs of male rat. *Mol Cell Endocrinol.* 95(1-2): 115–120.

142. Zhang J., Huang B., Hu G., Zhan X., Xie T., Li S., Zhang X., Li H., Ge R.S., Xu Y., 2018. Aldosterone Blocks Rat Stem Leydig Cell Development In Vitro. *Front Endocrinol (Lausanne).* 9: 4.

143. Lahimer M., Abou Diwan M., Montjean D., Cabry R., Bach V., Ajina M., Ben Ali H., Benkhalifa M., Khorsi-Cauet H., 2023. Endocrine disrupting chemicals and male fertility: From physiological to molecular effects. *Front Public Health.* 11: 1232646.

144. Anway M.D., Leathers C., Skinner M.K., 2006. Endocrine disruptor Vinclozolin induced epigenetic transgenerational adult-onset disease. *Endocrinology.* 147: 5515–5523.

145. Ho S.-M., Tang W.-Y., de Frausto J.B., Prins G.S., 2006. Developmental exposure to estradiol and bisphenol A increases susceptibility to prostate carcinogenesis and epigenetically regulates

phosphodiesterase type 4 variant 4. *Cancer Res.* 66: 5624–5632.

146. Van Cauwenbergh O., Di Serafino A., Tytgat J., et al., 2020. Transgenerational epigenetic effects from male exposure to endocrine-disrupting compounds: a systematic review on research in mammals. *Clin Epigenet.* 12: 65.

147. Roelofs M.J.E., van den Berg M., Bovee T.F.H., Piersma A.H., van Duursen M.B.M., 2015. Structural bisphenol analogues differentially target steroidogenesis in murine MA-10 Leydig cells as well as the glucocorticoid receptor. *Toxicol.* 329: 10–20.

148. Molina-Molina J.M., Amaya E., Grimaldi M., Sáenz J.M., Real M., Fernández M.F., Balaguer P., Olea N., 2013. In vitro study on the agonistic and antagonistic activities of bisphenol-S and other bisphenol-A congeners and derivatives via nuclear receptors. *Toxicol Appl Pharmacol.* 272(1): 127–136.

149. Brander S.M., Gabler M.K., Fowler N.L., Connon R.E., Schlenk D., 2016. Pyrethroid pesticides as endocrine disruptors: molecular mechanisms in vertebrates with a focus on fishes. *Environ. Sci. Technol.* 50: 8977–8992.

150. Sidorkiewicz I., Zareba K., Wolczynski S., Czerniecki J., 2017. Endocrine-disrupting chemicals: Mechanisms of action on male reproductive system. *Toxicol Ind Health.* 33: 601–609.

151. Ding Z., Shen J.Y., Hong J.W., Zhang R., Li Z., Wang Q., Zhang J.P., Zhang M.R., Xu L.C., 2020. Inhibitory effects of cypermethrin on interactions of the androgen receptor with coactivators ARA70 and ARA55. *Biomed Environ Sci.* 33(3): 158–164.

152. Kasai M., Guerrero-Santoro J., Friedman R., et al., 2003. The Group 3 LIM domain protein paxillin potentiates androgen receptor transactivation in prostate cancer cell lines. *Cancer Res.* 63: 4927–4935.

153. Wu Q., Chambliss K., Umetani M., Mineo C., Shaul P.W., 2011. Non-nuclear estrogen receptor signaling in the endothelium. *J Biol Chem.* 286: 14737–14743.

154. Chen H., Xiao J., Hu G., Zhou J., Xiao H., Wang X., 2002. Estrogenicity of organophosphorus and pyrethroid pesticides. *J. Toxicol. Environ. Health A.* 65: 1419–1435.

155. Go V., Garey J., Wolff M.S., Pogo B.G., 1999. Estrogenic potential of certain pyrethroid compounds in the MCF-7 human breast carcinoma cell line. *Environ Health Perspect.* 107: 173–177.

156. Kim I.Y., Shin J.H., Kim H.S., Lee S.J., Kang I.H., Kim T.S., Moon HJ., Choi KS., Moon A., Han SY., 2004. Assessing estrogenic activity of pyrethroid insecticides using in vitro combination assays. *J Reprod Dev.* 50: 245–255.

157. Han Y., Xia Y., Han J., Zhou J., Wang S., Zhu P., Zhao R., Jin N., Song L., Wang X., 2008. The relationship of 3-PBA pyrethroids metabolite and male reproductive hormones among non-occupational exposure males. *Chemosphere.* 72: 785–790.

158. Dumasia K., Kumar A., Kadam L., Balasinor N.H., 2015. Effect of estrogen receptor subtype-specific ligands on fertility in adult male rats. *J Endocrinol.* 225: 169–180.

159. Saito K., 2000. Lack of significant estrogenic or antiestrogenic activity of pyrethroid insecticides in three in vitro assays based on classic estrogen receptor alpha-mediated mechanisms. *Toxicol Sci.* 57(1): 54–60.

160. Varayoud J., Monje L., Bernhardt T., Muñoz-de-Toro M., Luque E.H., Ramos J.G., 2008. Endosulfan modulates estrogen-dependent genes like a non-uterotrophic dose of 17beta-estradiol. *Reprod Toxicol.* 26(2): 138–145.

161. Mathur P.P., Selvaraju V., 2011. Effects of methoxychlor on male reproduction. In: Srivastava U.C., Kumar S., editors. *Emerging Trends in Zoology.* 1st ed. Narendra Publishing House; 409-422.

162. Danzo B.J., 1997. Environmental xenobiotics may disrupt normal endocrine function by interfering with the binding of physiological ligands to steroid receptors and binding proteins. *Environ Health Perspect.* 105: 294–301.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(2), 3036-3057 | ISSN:2251-6727

163. Pavlíková N., Bláhová L., Klán P., Sreenivas Reddy B., 2011. Enantioselective effects of alpha-hexachlorocyclohexane (HCH) isomers on androgen receptor activity in vitro. *Chemosphere.* 86(1): 65–69.

164. Hazarika J., Ganguly M., Borgohain G., Sarma S., Bhuyan P., Mahanta R., 2021. Disruption of androgen receptor signaling by chlorpyrifos (CPF) and its environmental degradation products: a structural insight. *J Biomol Struct Dyn.* 1–12.

165. Tamura H., Maness S.C., Reischmann K., Dorman D.C., Gray L.E., Gaido K.W., 2001. Androgen receptor antagonism by the organophosphate insecticide fenitrothion. *Toxicol Sci.* 60(1): 56–62.

166. Erthal R.P., Siervo G.E.M de L., Frigoli G.F., Zaninelli T.H., Verri W.A., Fernandes G.S.A., 2022. Malathion exposure during juvenile and peripubertal periods downregulates androgen receptor and 17-β-HSD testicular gene expression and compromises sperm quality in rats. *J Dev Orig Health Dis.* 14(2). Published online.

167. Bal R., Nazirog˘lu M., Türk G., Yilmaz Ö., Kulog˘lu T., Etem E., et al., 2012. Insecticide imidacloprid induces morphological and DNA damage through oxidative toxicity on the reproductive organs of developing male rats. *Cell Biochem. Funct.* 30: 492–499.

168. Bagri P., Kumar V., Sikka A., 2015. An in vivo assay of the mutagenic potential of imidacloprid using sperm head abnormality test and dominant lethal test. *Drug Chem. Toxicol.* 38: 342–348.

169. Yuan X., Shen J., Zhang X., Tu W., Fu Z., Jin Y., 2019. Imidacloprid disrupts the endocrine system by interacting with androgen receptor in male mice. *Sci Total Environ.* Article 135163.

170. Yasunaga R., Ikuta J., Murata Y., Inoue K., Koga H., Masaki T., Tamura H., 2013. Ligand-independent androgen receptor antagonism caused by the newly developed pesticide pyrifluquinazon (PFQ). *Reprod Toxicol.* 35: 1–6.

171. Andersen H.R., Vinggaard A.M., Rasmussen T.H., Gjermandsen I.M., Bonefeld-Jørgensen E.C., 2002. Effects of currently used pesticides in assays for estrogenicity, androgenicity and aromatase activity in vitro. *Toxicol. Appl. Pharmacol.* 179: 1–12.

172. Molina-Molina J.M., Hillenweck A., Jouanin I., Zalko D., Cravedi J.P., Fernandez M.F., Pillon A., Nicolas J.C., Olea N., Balaguer P., 2006. Steroid receptor profiling of vinclozolin and its primary metabolites. *Toxicol Appl Pharmacol.* 216: 44–54.

173. Amato C.M., Boyd M., Yang J., McCoy K.A., 2018. Organizational effects of the antiandrogen, vinclozolin, on penis development in the mouse. *Biol Reprod.* 99(3): 639–649.

174. Grad J.M., Dai J.L., Wu S., Burnstein K.L., 1999. Multiple androgen response elements and a Myc consensus site in the androgen receptor (AR) coding region are involved in androgen-mediated up-regulation of AR messenger RNA. *Mol Endocrinol.* 13: 1896–911.

175. Selvakumar K., Sheerin Banu L., Krishnamoorthy G., Venkataraman P., Elumalai P., Arunakaran J., 2011. Differential expression of androgen and estrogen receptors in PCB (Aroclor 1254)-exposed rat ventral prostate: Impact of alpha-tocopherol. *Exp Toxicol Pathol.* 63(1-2): 105–12.

176. Jansen M.S., Nagel S.C., Miranda P.J., Lobenhofer E.K., Afshari C.A., McDonnell D.P., 2004. Short-chain fatty acids enhance nuclear receptor activity through mitogen-activated protein kinase activation and histone deacetylase inhibition. *Proc Natl Acad Sci U S A.* 101: 7199–7204.

177. Tirado O.M., Martínez E.D., Rodríguez O.C., Danielsen M., Selva D.M., Reventós J., Munell F., Suárez-Quian C.A., 2003. Methoxyacetic acid disregulation of androgen receptor and androgen-binding protein expression in adult rat testis. *Biol Reprod.* 68(4): 1437–1446.

178. Bagchi G., Hurst C.H., Waxman D.J., 2009. Interactions of methoxyacetic acid with androgen receptor. *Toxicol. Appl. Pharmacol.* 238(2): 101–110.

179. Sharpe R.M., Turner K.J., Sumpter J.P., 1998. Endocrine disruptors and testis development. *Environ Health Perspect.* 106: A220–1.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(2), 3036-3057 | ISSN:2251-6727

180. Eacker S.M., Shima J.E., Connolly C.M., Sharma M., Holdcraft R.W., Griswold M.D., Braun R.E., 2007. Transcriptional profiling of androgen receptor (AR) mutants suggests instructive and permissive roles of AR signaling in germ cell development. *Mol Endocrinol.* 21: 895–907.

181. Abu Zeid E.H., Alam R.T.M., Abd El-Hameed N.E., 2016. Impact of titanium dioxide on androgen receptors, seminal vesicles, and thyroid hormones of male rats: possible protective trial with aged garlic extract. *Andrologia.* 49(5): e12651.

182. Balló A., Busznyákné Székvári K., Czétány P., Márk L., Török A., Szántó Á., Máté G., 2023. Estrogenic and non-estrogenic disruptor effect of zearalenone on male reproduction: A review. *Int. J. Mol. Sci.* 24(2): 1578.

183. Gao Y., Zhao Y., Zhang H., Zhang P., Liu J., Feng Y., Men Y., Li L., Shen W., Sun Z., et al., 2019. Pubertal exposure to low doses of zearalenone disrupting spermatogenesis through ERα related genetic and epigenetic pathways. *Toxicol Lett.* 315: 31–38.

184. Liu Q., Wang Y., Gu J., Yuan Y., Liu X., Zheng W., Huang Q., Liu Z., Bian J., 2014. Zearalenone inhibits testosterone biosynthesis in mouse Leydig cells via the crosstalk of estrogen receptor signaling and orphan nuclear receptor Nur77 expression. *Toxicol. Vitr.* 28: 647–656.

185. Baker M.E., Katsu Y., 2020. Progesterone: An enigmatic ligand for the mineralocorticoid receptor. *Biochem. Pharmacol.* 177: 113976.

186. Wang Y., Li H., Zhu Q., Li X., Lin Z., Ge R.S., 2019. The cross talk of adrenal and Leydig cell steroids in Leydig cells. *J Steroid Biochem Mol Biol.* 192: 105386.