Bustani *et al.*
Reproductive Biology and Endocrinology (2025) 23:70
https://doi.org/10.1186/s12958-025-01401-3

Reproductive Biology and Endocrinology

REVIEW

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The aryl hydrocarbon receptor: a new frontier in male reproductive system

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Abstract

Background The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor historically recognized for its role in the regulation of toxicity mediated by environmental chemicals. Recent research points to AhR's critical participation in male reproductive physiology, particularly in spermatogenesis, hormone signaling, and the maintenance of sperm quality. Both endogenous ligands (e.g., dietary and gut microbiota-derived metabolites) and exogenous pollutants (e.g., dioxins and benzo-α-pyrene) influence AhR-mediated pathways, making it a key link between environmental exposures and male fertility.

Results This review highlights AhR's influence on the male reproductive system, emphasizing the role of endogenous AhR ligands and AhR expression in the maturation and function of male reproductive organs. Environmental AhR agonists have been shown to induce oxidative stress, hormonal imbalance, and sperm DNA damage, which impact harmfully on the spermatogenesis process, which leads to reproductive abnormalities. Conversely, certain natural compounds such as resveratrol, curcumin, and lycopene appear to antagonize AhR activation and reduce its negative effects, thus offering potential protective benefits against male reproductive toxicity. Nevertheless, discrepancies persist regarding the exact interplay between AhR signaling and critical reproductive hormones such as testosterone and LH, and it remains unclear how transgenerational epigenetic changes triggered by AhR activation might affect long-term male fertility.

Conclusion AhR is pivotal in male reproductive physiology, influencing spermatogenesis, sperm quality, and hormone regulation through its interactions with both endogenous and environmental ligands. Persistent pollutants such as dioxins and polycyclic aromatic hydrocarbons cause oxidative damage and hormonal disturbances via AhR, contributing to reduced sperm quality and fertility.

Keywords AhR, Spermatogenesis, Spermiogenesis, Male fertility

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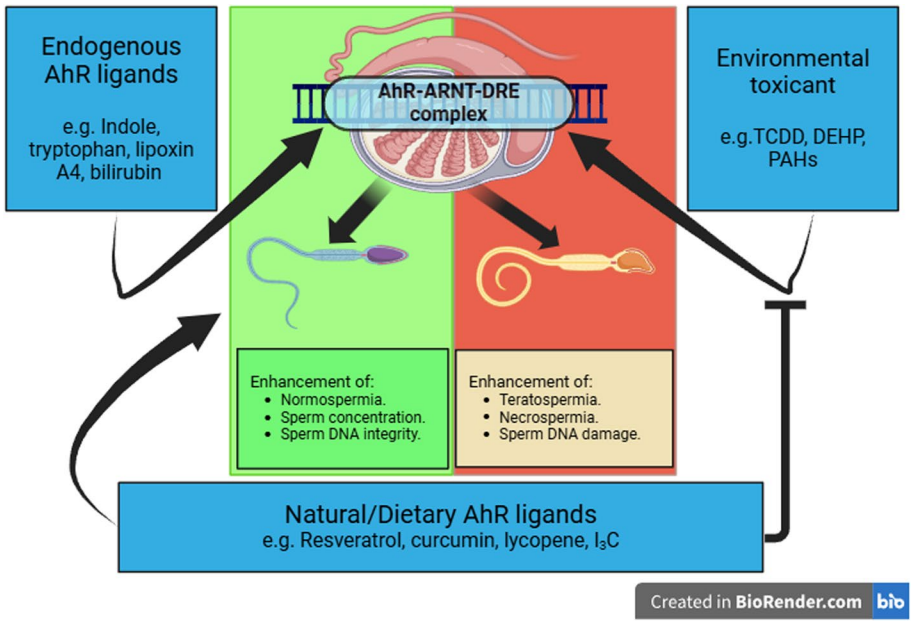
Graphical Abstract

The Impact of ligands of Aryl Hydrocarbon Receptor (AhR) on Male Reproductive Health. →, activation; ⊣, inhibition; DEHP, Di(2-ethylhexyl) phthalate; I3C, indole-3-carbinol; PAH, polycyclic aromatic hydrocarbon; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin (Created by Biorender.com).



Introduction

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that connects various external stimuli, including environmental, dietary, microbial, and metabolic. The AhR regulates transcriptional programs in a ligand-specific, cell-type-specific, and context-specific manner [1]. Scientific research has elucidated the complexities of AhR's structure and function since the first report on identifying the AhR was published in 1976 [2]. Despite decades of research on the AhR, its precise functions in male reproductive biology remain incompletely understood and sometimes contradictory. Since then, the biological effects of AhR have been extensively studied across various physiological functions such as the nervous system [3, 4], immune system [5, 6], digestive system [7, 8], hepatic function [9–11], respiratory system [5, 12, 13], renal system [14, 15], skin health [16], and others [17]. Moreover, the complex network of AhR extends its influence on the realm of reproduction, adding another layer of complexity to its biological significance. However, findings often diverge regarding whether AhR activation promotes or inhibits male germ cell development. It impacts the intricate cellular processes involved in reproduction, playing a pivotal role in fertility, embryonic development, and hormone signaling. While different studies report detrimental effects (e.g., reduced sperm counts, disrupted hormone levels, or testicular pathology following AhR ligand exposure), others highlight AhR's protective or homeostatic roles through its endogenous ligands and crosstalk with various signaling pathways [18–20]. The interaction of AhR with endogenous and exogenous ligands modulates gene expression and contributes to the delicate balance of reproductive functions [18–20]. Investigating the relationship between AhR and reproductive processes not only enhances our understanding of fertility, reproductive disorders, and the impact of environmental factors on reproductive health but also unveils the intricate molecular mechanisms underlying critical aspects of life.

That critical gap relates to the interplay between AhR and other hormone receptors, such as androgen and estrogen receptors. AhR can antagonize or augment these signals through direct protein–protein interactions or co-occupancy at shared response elements on DNA, leading to uncertain net effects on testosterone production, luteinizing hormone levels, and Sertoli cell function. There has been a limited number of reviews on the role of AhR in the regulation of the male reproductive

system. As the new role of AhR is becoming recognized, we believe that a timely review that explores its role in male reproductive systems is warranted. To this end, this review provides an overview of AhR's structure, function, and signaling pathways. Additionally, we consider its impact on male reproductive health and disorders, focusing on the influence of environmental factors, and identifying potential therapeutic applications in these areas.

Aryl hydrocarbon receptor

The AhR is a diverse and dynamic cytosolic receptor with expression in an extensive range of tissues throughout both developmental stages and adulthood [21]. Its widespread presence underscores its crucial nature in myriad biological processes, highlighting its role as a key regulator in maintaining homeostasis and responding to environmental cues [22]. The varied expression of AhR across tissues and life stages provides solid evidence of its involvement in vital physiological functions, suggesting its role in orchestrating complex biological systems [23]. Renowned as a transcription factor, AhR is activated by ligands and holds significant importance in an array of physiological functions such as xenobiotic metabolism, cellular proliferation, and developmental pathways. Notably, its importance has been reaffirmed in the field of reproductive studies thanks to its crucial regulatory functions [24].

History of aryl hydrocarbon receptor discovery

The aryl hydrocarbon receptor (AhR) was initially characterized in the 1970 s when researchers investigated the toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) [25, 26]. The human AhR cDNA was identified in 1993, as being expressed at the highest levels in the placenta, lungs, and heart [27]. Although first recognized as a key mediator of xenobiotic metabolism (e.g., driving cytochrome P450 induction), more recent work has highlighted AhR's influence on reproductive processes and immune regulation [28–32].

Human epidemiological evidence linking AhR to male reproductive outcomes

The most notable human data that discusses the relationship between AhR and reproductive toxicity began in 1976 following Seveso chemical explosion in Italy, which exposed residents to extremely high levels of TCDD [33] Subsequent epidemiological follow-ups revealed several long-term health impacts, including changes in sex ratios (fewer male births) and reduced sperm quality in exposed men [34]. Additionally, the study noted decreases in sperm count, motility, and normal morphology, suggesting that acid-induced AhR activation contributed to these adverse effects on male fertility. Moreover, evidence arises from occupational exposure studies; the men working in industries with high dioxin or polycyclic aromatic hydrocarbon (PAH) exposure (e.g., aluminum smelting, steel production, or pesticide manufacturing) have shown altered semen parameters and, in some cohorts, lower testosterone levels or gonadotropin imbalances [35].

Outstanding questions in AhR-mediated male reproductive regulation

Despite the progress made so far, there remain several key uncertainties regarding how the AhR influences male reproductive biology. Also, a key question that remains to be addressed is whether germline epigenetic changes arising from AhR activation could be passed down through multiple generations. Yet another concern involves the degree to which chronic, low-level exposure to AhR ligands subtly affects hormone production and semen characteristics, and whether specific developmental windows—such as puberty or adulthood—are more vulnerable [28, 35]. Further complexities include the ways in which AhR may interact with other endocrine pathways and how dietary or microbial metabolites acting as AhR ligands might influence reproductive outcomes [29].

Structure of aryl hydrocarbon receptor

The AhR is a transcription factor that belongs to the basic helix-loop-helix Per-Arnt-Sim (bHLH-PAS) family. Its structure consists of three domains (Fig. 1) [36]: the core DNA-binding domain, the N-terminal PAS domain, and the C-terminal ligand-binding domain [37, 38]. Combined, these domains give the AhR the capacity to bind ligands, regulate gene expression, and recognize environmental stimuli [39].

To sense a wide array of ligands and initiate conformational changes that lead to AhR activation, the N-terminal bHLH/PAS domains are vital [37]. Furthermore, these domains facilitate the translocation of the ligand-bound AhR-ARNT complex into the nucleus, where it interacts with target gene promoters and binds to DNA [40]. Because of its complex ligand interactions, the central domain delicately manages gene expression by refining AhR's response to external stimuli [41].

Moreover, AhR possesses nuclear export signals (NES) and nuclear localization signals that dictate its movement between the cytoplasm and nucleus [42, 43]. Guided to the nucleus by the NLS, the AhR regulates gene expression. The NES consequently facilitates AhR's export from the nucleus, ensuring that transcriptional responses conclude promptly [44].

Trans-activation of transcription is achieved through the interaction of AhR's trans-activation domain (TAD) with co-activators, such as ARNT, CBP/p300, and SRC-1.

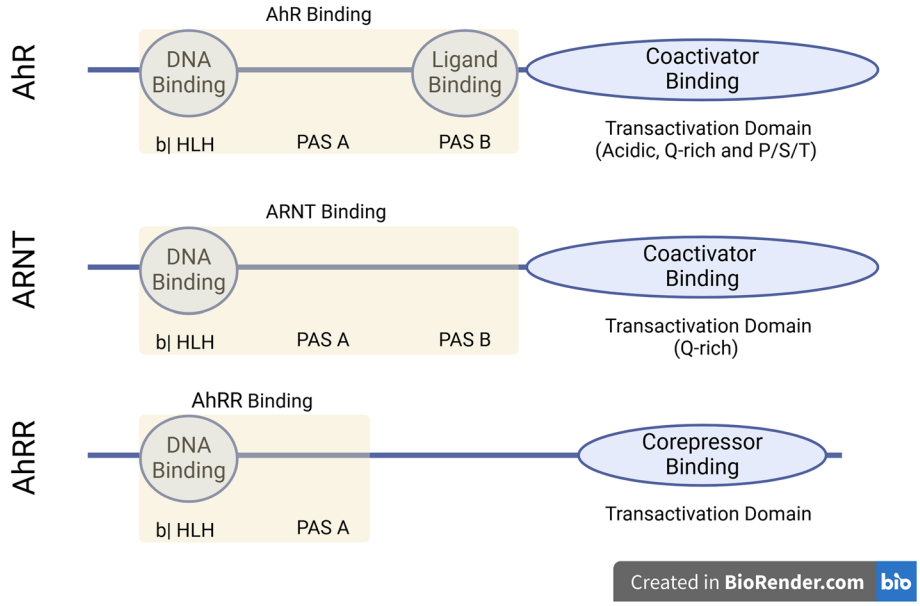


Fig. 1 The functional domains of the AhR, ARNT and AhRR proteins**:** AhR domain structure; PAS: Per-Arnt-Sim (A and B); Q-rich: glutamine; S/T/P: serine, threonine & proline [36]

Through the dynamic modulation of the TAD's activity by post-translational modifications like phosphorylation and acetylation of histones, AhR can tailor gene expression responses to different cellular contexts and enhance gene transcription.

Understanding of AhR's three-dimensional structure and ligand-binding pockets has been advanced by structural studies, including homology modeling and ligand docking experiments. These studies have also illuminated the molecular mechanisms that allow AhR's flexible ligand-binding capacity [45, 46]. In-depth investigations reveal the complex nuances of these conformational shifts, which are critical for AhR activation and subsequent gene transcription. These conformational alterations are prompted by ligand binding.

When AhR is idle, it is usually positioned in the cytosol where it is associated with a cluster of chaperone proteins that maintains its stability and prevent its degradation [47, 48]. This stable form of AhR in the cytosol, identified as the AhR-low activity variant, displays a diminished responsiveness to ligand activation [41].

Cytosolic aryl hydrocarbon receptor

Under normal physiological conditions, the AhR is naturally found in an idle mode in the cytosol of various cells. This status is also known as the AhR-low activity variant, which is less responsive to activation by ligands [49]. In its stable cytosolic form, the AhR is associated with a complex of chaperone proteins, including AhR-interacting protein (AIP), Heat shock protein 90 (HSP90), Prohibitin 23 (p23), and X-associated protein 2 (XAP2). These proteins help maintain its structural integrity and prevent its degradation in the absence of ligand binding. Furthermore, the stabilization of AhR within the cytoplasm, which prevents unliganded nucleocytoplasmic shuttling, protects AhR from degradation by the ubiquitin–proteasome pathway, as illustrated in Fig. 2 [50].

Aryl hydrocarbon receptor repressor

The *aryl hydrocarbon receptor repressor* (*AhRR*) has been identified as a target gene of AhR, providing a unique mechanism of feedback inhibition of AhR function where the transcription factor directly induces the expression of its repressor through binding to its cognate regulatory sequence located in the promoter of the target gene. The N-terminal portion of the AhRR protein shows significant structural resemblance to AhR, particularly housing the DNA-binding bHLH domain and the PAS-A domain (Fig. 1). However, the C-terminal segment lacks the PAS-B and Q-rich TADs, suggesting that AhRR does not possess the well-defined AhR ligand-binding domain and remains transcriptionally inactive. AhRR expression is regulated by one or more xenobiotic response elements (XREs) found in the enhancer/promoter sequence of the murine and human *Ahrr* gene. AhRR can dimerize with ARNT and function as a specific inhibitor of AhR activity by competing with AhR to form heterodimers with ARNT, thus preventing the binding and trans-activation of AhR/ARNT complexes via XREs (Fig. 3) [51]. The ability of AhRR to regulate AhR's signaling in major cellular

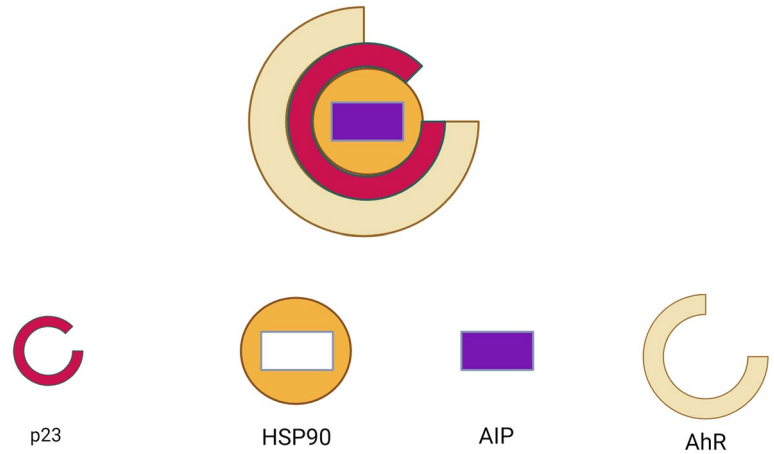


Fig. 2 The AIP/AhR/Hsp90/p23 complex. AhR: Aryl hydrocarbon receptor; AIP: Aryl hydrocarbon receptor-interacting protein; Hsp: Heat shock protein Hsp90-AhR-p23 complex [50]

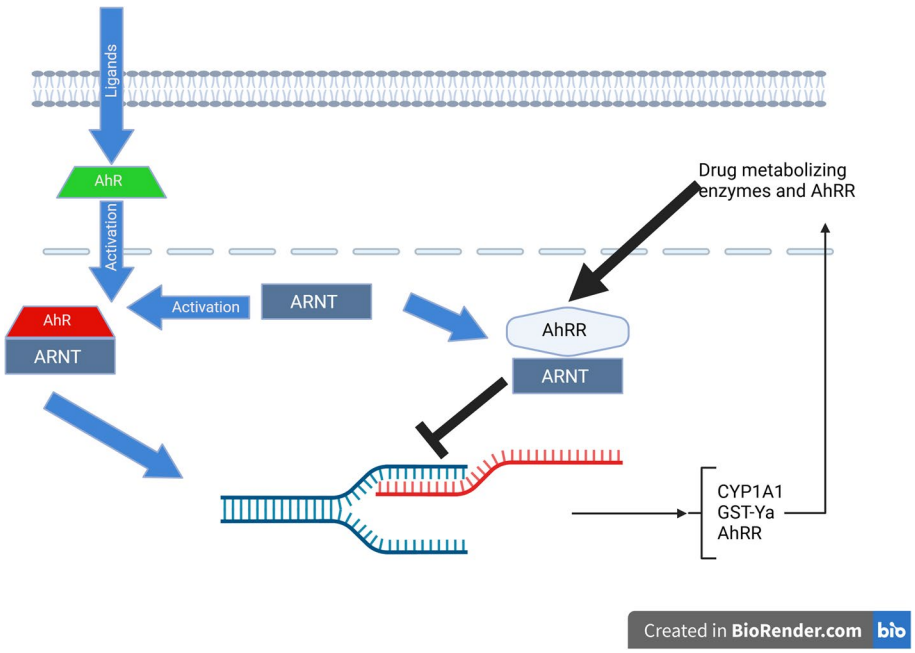


Fig. 3 Schematic illustration of the repression of the canonical AhR signaling pathway by AhRR [51]

processes like cell cycling, inflammation, and apoptosis is complex and varies depending on the cellular and environmental context. Moreover, in vitro experiments with multiple distinct types of cancer cell lines indicated that AhRR acts as a tumor suppressor gene [52]. Notably, a recent investigation uncovered numerous unique DNA binding sites within the promoter regions of tumor suppressor genes and genes associated with cancer development, specifically targeted by AhRR [53]. Additionally, human studies found epigenetic modifications of AhRR's regulatory region associated with exposure to cigarette smoke and the development of various cancer types [54]. Conversely, a study found that overexpressing AhRR in a transgenic mouse model led to the induction of Cytochrome P450 1 A1 (CYP1 A1) by TCDD in a tissue-specific manner and that the overexpression of AhRR protected against hepatic injury and acute TCDD toxicity. CYP1 A1 is known for its involvement in the bioactivation of certain procarcinogens, converting them into more reactive forms capable of binding to DNA and

potentially causing mutations. Thus, in the mouse model, overexpression of AhRR protected the mice from cancer development by preventing TCDD from activating CYP1 A1 [55, 56].

Aryl hydrocarbon receptor nuclear translocator

The AhR nuclear translocator (ARNT) is a protein that is essential for the function and comprehensive regulatory network of the AhR signaling pathway [57]. When AhR is activated in the cytoplasm, and the appropriate compounds bind within the AhR's PAS domain, there are conformational changes and nuclear localization signals are unmasked [58]. Subsequently, AhR is translocated into the nucleus, where it is heterodimerized with ARNT. The transcriptionally active AhR/ARNT complex binds to XREs within the regulatory region of target genes to initiate transcription [39].

The ARNT is made up of a bHLH domain necessary for DNA binding, two essential PAS domains (PAS-A and PAS-B) for dimerization, and one trans-activation domain that enables its dimerization with AhR and binding to XREs [59]. The nuclear localization signal plays a role in oxygen sensing and cellular adaptation to hypoxic conditions, earning it the alternative name of HIF-1β [60]. ARNT operates at the intersection of multiple signaling pathways, contributing to the fine-tuning of AhR-mediated responses. ARNT features characteristic PAS domains and a bHLH motif, which facilitates its dimerization with AhR and binding to XREs [39].

AhR activation mechanisms (ligand activation to gene expression)

The AhR was frequently referred to as the "dioxin receptor" due to early detection of its role in regulating toxic responses to environmental pollutants including dioxins. However, recent advancements have unveiled its multifaceted role in regulating immunity, cell proliferation, and differentiation [61]. Moreover, the activation of AhR is a complex process comprising several steps:

Endogenous role of AhR

AhR-null mouse models suggest that AhR has a role in liver development: the livers of AhR-null mice tend to be smaller, with portal fibrosis, premature lipid accumulation, and further changes leading to the differential expression of hundreds of genes [62, 63]. Moreover, another study revealed that AhR deficiency exhibits sex-dependent defects in rats [64], while AhR knockout mice show unregulated matrix remodeling [65] and various cardiac dysfunctions [66]. Hence, it appears that AhR participates in the development of the liver, ovaries, cardiovascular system, immune system, and kidney formation in mammals [67]. The AhR has also been identified in early metazoans and multiple invertebrate species like *Drosophila melanogaster* and *Caenorhabditis elegans*, where it contributes to neuronal development [68]. Interestingly, invertebrate AhR orthologues do not seem to bind toxic AhR ligands, such as TCDD [69]. There are multiple candidate endogenous AhR ligands, including indoles, which are produced from dietary tryptophan by gut bacteria, and amino acid metabolites like prostaglandins and lipoxins; or tetrapyrroles, like bilirubin and biliverdin, 6-formyl (3,2-b) carbazole (FICZ), and 2-(1'H-indole-3-carbonyl) thiazole-4-carboxylic acid methyl ester (ITE), etc. [70]. Furthermore, indole-3-carbinol (I3 C) is another indole found in high concentration in cruciferous vegetables such as broccoli, cabbage and cauliflower and serves as an agonist of AhR which leads to downregulation of estrogen metabolism in estrogen-related cancers [71]; and ameliorates the colitis outcomes through modulation of mucin production [72]. However, although these compounds have been shown to bind AhR and trigger the expression of AhR target genes in most cases, their actual in vivo significance necessitates further investigation.

One of the most intriguing internal functions of AhR appears to be the modulation of cell proliferation in situations devoid of xenobiotic binding. Studies involving AhR-null mouse embryonic fibroblasts have demonstrated that AhR promotes progressive cell cycle activity even in the absence of an exogenous ligand [25, 73]. Conversely, low levels of TCDD can inhibit DNA synthesis in mouse epithelial cell cultures, rat primary hepatocytes [58, 69], or in rat liver following partial hepatectomy [74]. Consider, for instance, rat hepatoma 5L (AhR-positive) and BP8 (AhR-negative) cells. It has been observed that 5L cells proliferate more rapidly than BP8 cells [25, 58, 69]; furthermore, TCDD exposure induces G1 arrest in 5L cells but does not affect the proliferation of BP8 cells. This cell cycle arrest is linked to an increased expression of the cyclin-dependent kinase 2 (CDK2) inhibitor p27kip1, which in turn prevents the phosphorylation of pRb and subsequent activation of the E2 F transcription factor, a component that governs genes crucial for entry into the S-phase and DNA replication. Additional findings indicate that AhR directly interacts with pRb and represses the E2 F-dependent transcription in hepatoma cells [75–77].

Conversely, in contact-inhibited rat liver epithelial cells, AhR ligands cause an opposing effect—the loss of contact inhibition, leading to elevated cell proliferation. This loss of contact inhibition is also an AhR-dependent event [78–81]. Up-regulation of cell proliferation in confluent WB-F344 rat liver progenitor cells exposed to AhR ligand correlates with increased expression of cyclin A and heightened cyclin A/cdk2 activity [79]. In cells that are not exposed during contact inhibition, *cyclin A* gene

expression is suppressed along with cdk2 activity and cell proliferation [77]. Thus, AhR may have a dual role in cell cycle regulation: its activation might either promote proliferation or act against it, depending on circumstances [82].

Ligands of aryl hydrocarbon receptor

The interaction between a ligand and a receptor is characterized by multiple variables, and the final cellular response depends on the combination of these variables. In other words, the activation of the receptor by two different compounds may result in not just a quantitatively different, but also qualitatively unique cellular response [21, 83–85].

The majority of AhR ligands are partial agonists. Partial agonists such as 2,3,3′,4,4′-pentachlorobiphenyl, and galangin possess a similar affinity as that of full agonists, though the inherent activity of a partial agonist is lower than a full agonist. Consequently, partial agonists can never elicit a maximal response, irrespective of whether a partial agonist occupies all receptors. Crucially, partial agonists perform as functional antagonists; when combined with a full agonist, a partial agonist lessens the full agonist's effect, thereby exhibiting antagonistic behavior [86, 87].

Aryl hydrocarbon receptor and the reproductive system

The 1976 Seveso chemical explosion in Italy exposed residents to elevated levels of TCDD, a toxic chemical compound known for its severe and long-lasting toxic effects. Moreover, TCDD is lipophilic, accumulates in fatty tissues, and has a long half-life in humans, which further exacerbates its impact on those exposed to it. Additionally, Kerger (2011) reported that the explosion caused chloracne and had potential long-term health consequences, including effects on cancer rates. Kerger further noted that the explosion led to altered dental development, changes in the sex ratio, and decreased sperm quality. Moreover, TCDD triggers a cascade of events that can disrupt sperm cell development [88]. TCDD exposure has been shown to interfere with several key steps, leading to reduced sperm production, impaired sperm motility, and other reproductive issues [89]. AhR modulation alters the expression of genes involved in spermatogenesis and sperm function [90]. The rodent studies confirmed that TCDD and similar AhR ligands disrupt multiple steps of spermatogenesis that range from spermatogonia proliferation and meiosis to final sperm maturation [24, 91]. Furthermore, the AhR-knockout mice showed abnormalities in seminiferous tubules, and reduced expression of protamine (Prm1/Prm2) and other spermatid-specific genes were consistently observed, which proved the AhR's regulatory role even in the absence of exogenous ligands [92].

Role of AhR in cell cycle stage

The seminiferous tubule in the testis houses a multitude of germ cells at distinct stages of development and maturation within the spermatogenic cycle. These spermatogenic cells produce mature spermatozoa, which are released into the tubular lumen as functional sperm through the process of spermatogenesis. Spermatogenesis is a complex, dynamic process during which spermatogonia proliferates, differentiates, and transforms into mature spermatozoa. This process occurs in three major stages: the mitotic stage, the meiotic stage, and the maturation stage [92].

Role of AhR in spermatocytogenesis (Interphase and Mitosis)

Interphase

Gap 1 phase The Gap 1 phase (pre-meiotic) is a critical stage in the development of male germ cells. This phase is characterized by the expression of specific genes that play a role in round spermatids. The Gap 1 phase is also associated with the formation of gap junctions, particularly those involving Cx43, which play a role in the synchronization of germ cell proliferation and differentiation [93, 94]. The role of AhR in the G1 phase of the cell cycle is intricate and context-dependent. The specifics of how AhR action, particularly without an exogenous ligand, promotes cell progression through the G1 phase remain unclear. Additionally, studies using AhR-defective cell line variants and AhR-null mouse embryonic fibroblasts suggest that cells lacking a functional AhR possess a prolonged doubling time, which can mainly be attributed to a delayed progression through the G1 phase [95]. Conversely, exposure to potent AhR ligands like TCDD inhibits G1 phase progression in various cell lines [95, 96]. TCDD-AhR-mediated inhibition of G1 phase progression involves increases in the levels of CDK2 and the inhibitor of p27 KIP1. Furthermore, the inhibition of CDK2 activity by p27 KIP1 leads to a stall in the cell cycle within the G1 phase [75, 97]. The impact of AhR on the cell cycle may differ based on the presence or absence of exogenous ligands and the specific cellular context [98]. Studies demonstrate that disruptions induced by AhR ligand lead to Cx43 degradation, which subsequently causes germ cell proliferation. This alters the differentiation and forms of round spermatids [79].

Synthesis phase (S-phase) At the synthesis phase, cells undergo DNA replication in preparation for cell division,

and it plays a pivotal role in maintaining the spermatogonia stem cell population, which is crucial for continuous sperm production [99]. Recent studies have indicated that AhR can contribute to the p300-mediated induction of DNA synthesis. Furthermore, AhR action in the absence of an exogenous ligand may expedite S-phase progression; however, exposure to the AhR ligand, such as TCDD, leads to the inhibition of DNA replication in various cell lines [69, 100, 101]. The presence of potent AhR ligands can tip the balance from a pro-proliferative role to an anti-proliferative outcome by altering expression of cell cycle regulatory genes and increasing metabolic enzyme expression (e.g., CYP1 A1), which influences the cell's redox state [69, 100, 101]. Additionally, research shows that TCDD treatment in animals reduces the number of cells in the S-phase and results in the accumulation of cells in the G1 phase [96]. From past studies, it appears that AhR plays a significant role in regulating the S-phase of the cell cycle [91]. Also, AhR activity, influenced by the presence or absence of its ligands and the metabolic activity of P4501 A1, is important in regulating cell cycle progression, particularly during the G1-to-S-phase transition. The alteration of cell cycle progression benefits from the manipulation of AhR activity and its subsequent effects on cell cycle regulators.

Gap 2 phase The specific role of AhR during the Gap 2 (G2) phase of the cell cycle is not yet well-defined. During the G2 phase, the cell checks itself for any DNA damage following replication, using a control mechanism known as the G2-M DNA damage checkpoint. This provides the cell with a period to correct potential errors in its genome before cell division [102]. Aurora kinase A, a serine/threonine kinase, plays a critical role in facilitating the transition from the G2 phase to mitosis. Recent studies have demonstrated that Aurora kinase A, which is integral to the regulation of the G2/M checkpoint, exhibits dysregulated expression in Aryl Hydrocarbon Receptor (AhR) knockout models (Jones et al., 2021). These findings suggest that AhR may indirectly safeguard genomic integrity during the G2 phase; however, further investigations are required to fully elucidate the mechanisms underlying this process, especially in germ cells [103, 104].

Mitosis

Aurora kinase A promotes entry into mitosis by activating cyclin-dependent kinase 1, essential for the G2/M phase transition of the cell cycle. The specific role of AhR in the various phases of mitosis is not thoroughly studied, with limited information available. A prior study suggests that AhR influences the expression of Aurora kinase A, and its absence or antagonism leads to increased intracellular levels of Aurora kinase A, critical in mitosis, particularly in spindle formation and chromosome segregation [105]. AhR directly binds to DNA at AhR-responsive elements upstream of the *Aurora kinase A* gene's transcriptional start site. This binding potentially acts as a transcriptional regulator or enhancer controlling Aurora kinase A expression. Additionally, studies suggest that AhR plays a role in regulating the G2/M phase transition in hematopoietic stem and progenitor cells by influencing the expression of the key mitotic regulator, Aurora kinase A. Dysregulation of Aurora kinase A, as seen with altered AhR signaling, can impact the proliferative capacity of these cells and potentially contribute to diseases.

In prophase, chromosomes condense and become visible, the nuclear envelope disintegrates, and the mitotic spindle begins to form. AhR plays a crucial role in chromatin condensation regulation during prophase, the first stage of mitosis. Chromatin condensation comprises the compaction of DNA into a more organized structure, simplifying proper chromosome alignment and segregation in later stages [106]. Studies have shown that TCDD-AhR signaling upregulates histone deacetylases by enhancing chromatin compaction. Moreover, excessive compaction or mis-timed deacetylation, however, can impair accurate chromosome segregation [107]. This allows histones to wrap the DNA more tightly [108–110]. Lack of AhR correlates with increased Aurora Kinase A expression and faster progression through mitosis, whereas TCDD-bound AhR can paradoxically cause mitotic arrest in some contexts [24, 92]. Throughout metaphase, AhR contributes to chromosome alignment at the metaphase plate by enhancing the expression of microtubule-associated and kinetochore proteins, ensuring accurate chromosome segregation [111–113]. In anaphase, AhR facilitates sister chromatid segregation by triggering the expression of the anaphase-promoting complex and microtubule motor proteins. These facilitate chromatids' movement towards opposite poles [114–116]. During telophase, AhR is implicated in the reformation of the nuclear envelope and cytokinesis, bolstering the expression of nuclear envelope proteins, actin, and myosin filaments, generating two distinct daughter cells with intact nuclei and completing the mitotic process [117]. Despite AhR's importance in these mitotic stages, further research is required to fully grasp its regulatory mechanisms.

Meiosis (spermatogenesis)

Meiotic division I and II AhR is essential for managing meiosis during spermatogenesis [24]. During prophase I of meiotic division I, AhR activation has been linked to

the regulation of gene expression impacting the progression of this phase. It manages momentous events such as homologous chromosome pairing and recombination [89]. The effect of AhR on spindle formation and chromosome alignment becomes evident as cells transition into metaphase I, as AhR signaling may assist in the accurate separation of homologous chromosomes during anaphase I [24]. In the context of telophase I, AhR plays a role in the establishment of two distinct haploid cell gametes. Moreover, AhR continues to exert its influence in meiotic division II. In prophase II, AhR contributes to the maintenance of proper chromosomal arrangement and integrity [118].

During metaphase II, AhR contributes to the alignment of chromosomes along the equatorial plane. In anaphase II, it participates in preserving chromatid integrity during their orderly segregation. Furthermore, during telophase II, AhR likely aids in the completion of meiosis, leading to the formation of four haploid cells. In conclusion, AhR appears to be a significant molecular factor in orchestrating the complex processes of meiosis during spermatogenesis, securing the precise transmission of genetic information to the forthcoming generation [21, 89].

Most mechanistic insights come from rodent studies exposing males to TCDD or using AhR-null mice [21, 80, 95]. Human epidemiological data are more limited and generally rely on retrospective analysis of TCDD-exposed populations (e.g., Seveso) showing elevated rates of sperm abnormalities [33, 88].

Spermiogenesis

In spermiogenesis, which involves the transformation of spermatids into motile spermatozoa, the AhR plays a pivotal role spanning multiple distinct phases: the Golgi Phase, Cap Phase, Tail Phase, and Maturation Phase. During the Golgi Phase, AhR orchestrates the formation of the acrosome, a specialized organelle that contains enzymes essential for fertilization [119]. As the process transitions to the Cap Phase, AhR may help influence the reshaping of the nucleus and the positioning of the centriole, which are crucial for the subsequent formation of the sperm head and tail. In the Tail Phase, AhR potentially contributes to the development of the flagellum, ensuring proper motility of the mature sperm [120]. In the final Maturation Phase, AhR is likely involved in finalizing the structural and molecular modifications necessary for the sperm cell to achieve full functionality [21, 120–122].

Previous studies have displayed abnormalities in the seminiferous tubules of AhR knockout subjects. The expression of genes that are active during spermiogenesis, including Prm1 and Prm2, which encode protamine, was affected [119]. These protamine replace histones late in spermatogenesis and contribute significantly to sperm head condensation [123]. Hspa2 encodes a heat shock protein specifically expressed in spermatogenic cells, acting as a chaperone for the transition proteins that precede protamination. Disruption of HSPA2 is associated with poorly remodeled germ cells with residual mitochondria that generate increased reactive oxygen species. All three of these genes showed lower levels of expression in AhR knockout testes compared to wild-type testes [124].

Spermiation

Spermiation, the process by which mature sperms are released into the lumen of the seminiferous tubules, signifies the conclusion of spermatogenesis. AhR modulates the molecular and cellular events needed for the separation and liberation of mature sperm from Sertoli cells, facilitating the completion of spermatogenesis, including the disassembly of Sertoli–spermatid junctions, cytoskeletal remodeling, and the local regulation of growth factors and cytokines [125]. When AhR is activated by potent ligands, AhR induces enzymes as CYP1 A1 and alters junctional proteins as connexins in a way that disrupts normal spermiation, prematurely detaching immature spermatozoa and ultimately compromising sperm quality as showed in exposure to TCDD [91, 126]. In other rodent models, AhR knockout or ligand-induced activation correlates with abnormal protamine expression (Prm1, Prm2), dysregulated Aurora kinase A, and premature breakdown of actin-based cytoskeletal structures, leading to defective spermiation [24, 127]. In summary, the AhR appears to be a critical factor in steering spermiogenesis, taking an active role in the ordered evolution of sperm cells and their final discharge during spermiation [128].

Overall, AhR signaling—whether through potent exogenous ligands such as TCDD or via endogenous modulators—can alter the expression of cell-cycle regulators, structural proteins (e.g., Aurora Kinase A), and spermatid-specific genes (Prm1, Prm2, Hspa2). In vivo rodent evidence strongly supports the notion that overactivation of AhR by TCDD disrupts each major phase of spermatogenesis, from spermatogonia proliferation to the release of mature sperm. Although human data are less experimentally controlled, the Seveso cohort studies point to similar effects on sperm quality and overall reproductive health [33, 88]. A consistent theme is that ligand-independent AhR plays a permissive or positive role in normal germ cell development, whereas exogenous ligand-activated AhR (particularly with high-affinity toxicants like TCDD) often inhibits cell-cycle progression,

reduces sperm output, and alters sperm morphology. The precise outcomes can depend on factors such as ligand potency, timing of exposure, and species-specific differences in AhR signaling [21, 74, 95, 96, 100, 129, 130].

Exploring AhR signaling in male reproductive health

Reproduction is a crucial biological event, and any signs of threatened reproductive function provoke significant responses in the scientific community and public media [131]. Despite receiving comparatively less attention, male reproductive function is a concern in the Western world, with infertility affecting approximately 15% of all couples [132]. Studies using AhR knockout mice have demonstrated that AhR deficiency is associated with defects in the seminiferous epithelium, the presence of multinucleated giant cells, hypocellularity, apical sloughing, and an increased count of retained elongated spermatids [119]. Furthermore, the modification of the AhR pathway, through the use of agonists or antagonists has led to changes in spermatozoa morphology and acrosome integrity via the regulation of the *Dnah1* gene [90]. Table 1 summarizes some of AhR's agonists and antagonists that interfere with reproductive system function of males.

Hormonal control

Spermatogenesis is dependent on the pituitary hormone, follicle-stimulating hormone (FSH), and locally produced androgens in response to the luteinizing hormone. These hormones not only nurture oocytes but also produce steroid hormones that ensure optimal functioning conditions in the female reproductive system [175, 176]. Most AhR/steroid receptor interactions have been studied in human breast cancer and endometrial carcinoma cell lines [176]. In one study, the activation of AhR by xenobiotics was shown to prompt the degradation of the androgen receptor [177]. Another study demonstrated low fertility in AhR KO mice along with degenerative alterations in the testes, germ cell apoptosis, and a decreased number of early spermatids [178]. Most recently, work has been published demonstrating that the abolishment of AhR signaling led to a decline in LH levels in rat serum [90].

AhR interaction with steroid hormone receptors

Steroid hormones play critical roles in the regulation of both human and animal fertility. In particular, male androgens, such as testosterone, function as primary inducers of the development of primary and secondary genital organs, in addition to libido potency [179]. The interplay between AhR and steroid hormone receptors is pivotal in regulating diverse physiological processes. Disruptions in steroid hormone synthesis, activity, or metabolism have been associated with various male reproductive issues. These include varicocele, erectile dysfunction, and infertility [180]. Such disturbances also impact female reproductive processes, affecting follicular dysfunction and atresia [180]. Previous in vitro experiments showed the competitive binding of AhR-ARNT complexes in HEC-1 A human endometrial carcinoma cells. This inhibits the binding of estrogen receptor alpha (ER-alpha) to imperfect estrogen response elements (EREs) [181, 182]. The activation of AhR can modulate the activity of steroid hormone receptors, especially the estrogen receptor, with potential substantial effects on endocrine function and overall health. This implies a crosstalk between AhR and estrogen receptor signaling pathways. Furthermore, certain environmental chemicals can bind directly to steroid hormone receptors, mimicking their function, and potentially causing adverse effects on both wildlife and humans [58, 183].

In vivo, recent studies have demonstrated that AhR-dependent mechanisms inhibit the growth of estrogen receptor-positive breast cancer cells in mouse xenografts [184]. The activation of AhR by Carbidopa, decarboxylase inhibitor, induces nuclear localization, leading to an increase in AhR transcriptional activity—effects that are nullified by an AhR blocker [185]. Studies on porcine follicular cells indicated that TCDD exposure led to a reduction in estrogen and progesterone synthesis through the use of AhR or ER blockers [186]. Dioxin has been observed to cause reproductive abnormalities including endometriosis, teratogenesis, abortion, decreased fertility, and endocrine disruption, particularly in luteal and follicular steroidogenesis in an AhR-dependent manner [187]. Additionally, prior studies suggested that AhR activity is crucial for cell proliferation. The AhR signaling pathway acts as a critical transcription factor in trophectoderm cells, influencing the cell cycle by modulating genes targeted by AhR and potential genes involved in trophectoderm cell proliferation [188]. The interaction mediated by AhR with steroid hormone receptors significantly affects the regulation of endocrine function. Research suggests that AhR can inhibit estrogen signaling by attaching to estrogen-responsive elements and accelerating estrogen receptor degradation [189]. This interaction can result in modified hormone synthesis, increased ligand metabolism, reduced receptor levels, and interaction between AhR and steroid hormone signaling pathways at the transcriptional level [190]. A recent study revealed that administering resveratrol, which is considered to be an AhR agonist, to male rats enhances the steroidogenesis of the testosterone hormone [90].

Table 1 Overview of aryl hydrocarbon receptor (AhR) ligands and their effects on spermatogenesis and hormonal control

AhR Ligand		Impact on Spermatogenesis	Impact on Hormonal Control	References
Endogenous (Candidate) AhR Ligands	indole-3-carbinol	Modulate AhR and protect testicular tissue from oxidative damage, improving and maintaining spermatogenesis furthermore protective effects against chemically induced testicular injury	Indoles influence estrogen metabolism, which indirectly affect androgen/estrogen balance	[133–135]
	Prostaglandins	Through the activation of AhR that influences gene expression related to immune and inflammatory processes within testicular tissue. Excess inflammatory signaling may impair spermatogenesis, whereas balanced prostaglandin signaling can be supportive. Balanced prostaglandin levels support normal spermatogenic progression, whereas elevated or dysregulated prostaglandin signaling contribute to impaired spermatogenesis	From activation of the AhR signaling pathway it modulates gonadotropin release and local testicular hormone synthesis. Abnormal prostaglandin levels correlate with altered testosterone, LH/FSH signaling	[136–139]
	Lipoxins A4	Through AhR pathway, it quell testicular inflammation. By reducing the local inflammatory response through AhR-mediated gene regulation, they protect Sertoli cells and support normal germ cell development. This anti-inflammatory, AhR-linked action helps maintain the blood–testis barrier and promotes healthier spermatogenesis	Although their direct binding affinity to AhR remains under investigation, lipoxins are thought to modulate AhR-regulated processes that affect steroidogenic enzymes and inflammatory mediators in the testis. By preventing chronic inflammation and preserving Leydig cell function, lipoxins indirectly help stabilize testosterone production. This AhR-associated resolution of inflammation thus safeguards normal hypothalamic–pituitary–gonadal axis signaling and hormone balance	[140–143]
	Bilirubin	Through AhR-mediated effects on spermatogenesis, which protects against oxidative stress that induced damage in the testis	Minimal direct effects on gonadotropins or testosterone reported; its primary relevance may be via antioxidant and anti-inflammatory mechanisms	[144, 145]
	6-formyl (3,2-b) carbazole	By activating AhR-dependent gene expression, FICZ can modulate cellular processes vital for germ cell maintenance, including proliferation and differentiation pathways in the testis. Moreover, regulatory effects on inflammation and oxidative stress play a protective and supportive role in sustaining normal germ cell development	Through its potent activation of AhR, it induces expression of cytochrome P450 enzymes such as CYP1 A1, which are crucial for steroid hormone metabolism, and by modulating these enzyme levels, it influences local androgen and estrogen balance in the testis and has the potential to fine-tune testicular hormone production and endocrine homeostasis	[141, 143, 146]
	2-(1′H-indole-3-carbonyl)thiazole-4-carboxylic acid methyl ester (ITE)	ITF is high-affinity AhR ligand ITE's modulation of AhR-dependent gene expression that influences the local cellular environment is critical for germ cell development. By regulating genes linked to cell cycle control and detoxification, ITE maintains or dysregulates, potentially disrupting spermatogenesis	ITE activates the AhR-regulated cytochrome P450 enzymes, and ITE can alter local and systemic steroid metabolism, subsequently indirectly affecting testosterone levels and disturbing feedback mechanisms in the hypothalamic-pituitary–gonadal axis	[147–149]

Table 1 (continued)

AhR Ligand		Impact on Spermatogenesis	Impact on Hormonal Control	References
Partial Agonists	2,3,3′,4,4′-Pentachlorobiphenyl	It strongly binds to the AhR and activates it; AhR regulates genes involved in xenobiotic metabolism and can disrupt testicular cell function, which reduce sperm counts, impair spermatogenic progression, and induce structural abnormalities in seminiferous tubules by altering Sertoli and germ cell interactions	When bound to the AhR, it induces cytochrome P450 enzymes and modifies local and systemic metabolism of hormones, especially androgens which lead to lower testosterone levels and altered production of gonadotropins (LH and FSH), ultimately disturbing the hypothalamic–pituitary–gonadal axis	[150–153]
	Galangin	Galangin interacts with AhR in partial agonistic or antagonistic ways, which regulate gene expression involved in oxidative stress responses and cell cycle control, subsequently indirectly protecting germ cells and supporting spermatogenesis by reducing inflammation and oxidative damage within the testicular environment	By modulating AhR activity, galangin potentially influences the expression of cytochrome P450 enzymes responsible for steroid metabolism	[154–156]
Classical Exogenous (Environmental) AhR Ligands	TCDD	A potent AhR agonist known to severely disrupt spermatogenesis, causing testicular lesions, reduced sperm counts, and altered seminiferous tubule structure in animal studies	Interferes with steroidogenesis and gonadotropin release, lowering testosterone levels and altering hypothalamic–pituitary–gonadal axis signaling	[33, 69, 100, 101, 157]
	Benzo-α-pyrene	It is a potent AhR ligand known to induce oxidative stress and DNA damage within the testes that by engaging AhR-dependent pathways and enhancing cytochrome P450 (CYP1) enzyme activity, it can disrupt germ cell development, reduce sperm quality, and impair seminiferous tubule integrity	Through its strong affinity for AhR, benzo-α-pyrene alters steroidogenic enzyme expression particularly in Leydig cells that lead to decreased testosterone production	[158–162]
	Polycyclic Aromatic Hydrocarbons (PAHs)	Similar to benzo-α-pyrene, many PAHs adversely affect spermatogenesis, increasing testicular oxidative stress and DNA damage	Often disrupt endocrine function by activating AhR-mediated gene expression and altering steroid hormone metabolism	[31, 163, 164]
	Phthalates	It interacts with AhR, contributing to adverse testicular outcomes such as reduced sperm quality and disrupted seminiferous tubule architecture since activating AhR-regulated genes and promoting oxidative stress, phthalates diminish germ cell viability and perturb Sertoli cell function, leading to impaired spermatogenesis	Phthalates also interfere with Leydig cell steroidogenesis through AhR-mediated changes in cytochrome P450 enzyme expression, often resulting in reduced testosterone levels. This disturbance in androgen production disrupts the hypothalamic–pituitary–gonadal axis, affecting both LH and FSH release and contributing to broader endocrine imbalances	[165, 166]

Table 1 (continued)

AhR Ligand		Impact on Spermatogenesis	Impact on Hormonal Control	References
Natural Compounds	Resveratrol	Resveratrol acts as a modulator of the AhR that partially antagonizes or regulates AhR-mediated gene expression; resveratrol reduces oxidative stress and inflammation in testicular tissue, and its protective microenvironment supports germ cell survival and maturation, leading to improved sperm parameters such as count, motility, and morphology	Through its influence on AhR signaling, resveratrol alters the expression of cytochrome P450 enzymes involved in steroid metabolism, potentially stabilizing testosterone levels. This modulation of androgen metabolism and feedback loops support the normal function of the hypothalamic-pituitary–gonadal axis	[90, 107, 167]
	Curcumin	Curcumin interacts with the AhR to regulate inflammation and oxidative stress pathways, which modulates AhR-mediated gene expression in testicular cells; curcumin lowers inflammatory cytokine production and prevents excess reactive oxygen species	Through partial agonism or antagonism of AhR, curcumin influences cytochrome P450 enzymes that metabolize steroid hormones	[159, 168–171]
	Lycopene	Lycopene acts as a modulatory ligand for the AhR that, through its antioxidant properties and potential AhR-dependent gene regulation, lycopene reduces oxidative stress and inflammatory signals in the testis	By influencing AhR-regulated detoxification enzymes, lycopene indirectly stabilizes steroid metabolism and testosterone levels	[172–174]

AhR and the regulation of the hypothalamic-pituitary–gonadal (HPG) axis

Studies have demonstrated a significant reduction in FSH and LH during the preovulatory period in female rats exposed to TCDD or related AhR ligands. This strongly suggests that the AhR may be partly responsible for the dysregulation of the hypothalamic-hypophyseal axis, which regulates spermatogenesis and androgen biosynthesis [191, 192]. Furthermore, the activation of AhR-induced suppression of gonadotropin surges has been attributed to a decreased responsiveness of the hypothalamus to the positive feedback from estrogens, without influencing preovulatory serum estrogen levels [191, 193]. This suggests reproductive toxicity linked to AhR activation [58, 90, 194].

Experiments with exogenous Gonadotropin-Releasing Hormone (GnRH) indicate that TCDD-induced inhibition of gonadotropin surges may be due to insufficient production and/or release of GnRH, implying an impact of TCDD on the central nervous system [195]. The observed inhibition of gonadotropin surges is linked to a decrease in hypothalamus responsiveness to estrogen feedback. This hypothesis is backed by the reversal of TCDD effects with higher estrogen concentrations [189]. The intricate relationship between the two is further demonstrated by the interaction between aryl hydrocarbon and estrogen-mediated signaling pathways, as evidenced by the partial estrogen antagonist, tamoxifen [196]. The expression of AhR signaling pathway members, especially in areas of the brain that control reproductive functions, emphasizes the complexity of AhR involvement. The coincidence of *AhR* gene expression with that of Glutamic Acid Decarboxylase 67, vital for Gamma-Aminobutyric Acid synthesis, suggests its potential role in regulating GABAergic neurons influencing the onset of puberty and gonadotropin surges [58, 69, 100].

Additionally, research shows that low doses of TCDD expedite puberty and HPG axis maturation in female rats—a compelling indication of complex interaction [197, 198]. The antagonism between AhR and estrogen receptor (ER) signaling pathways plays a substantial role in the estrogen-sensitive pituitary gland. This is evident in the interaction between AhR and ERα in both prolactin-secreting and gonadotropin-secreting cells [199]. TCDD displays a variety of effects, such as preventing E2-induced prolactin expression, encouraging LH-ß and ERα mRNA expression, and restraining FSH mRNA in the pituitary [196]. Intriguingly, TCDD reduces the release of prolactin, potentially due to increased dopamine secretion [200]. Developmental stage sensitivity to TCDD is clear, as it lessens fetal gonadotropin production without affecting adults. The influence of TCDD on GnRH release and the calcium's role in mediating these effects amplify the intricate mechanisms involved [201]. Furthermore, TCDD changes the metabolism of the hypothalamus and pituitary gland, impacting lipoic acid content, ATP levels, and gonadotropin secretion [202]. Thyroid hormones, which the HPG axis regulates, are also influenced by TCDD, with conflicting findings observed on T4 and T3 levels. The TCDD-mediated induction of UDP-glucuronosyltransferase might contribute to decreased thyroid hormone levels [203].

Biological effects of AhR in male reproduction

The specific role of AhR in spermatogenesis has not been extensively studied, despite the well-established effects of AhR activation on cellular processes like the cell cycle, stem cell proliferation, and tissue differentiation [119]. It appears that AhR activity is crucial for cell proliferation and progression through the cell cycle [204, 205]. Conversely, some studies suggest that AhR signaling has anti-proliferative effects as its activation can induce cell cycle arrest at the G1/G0 phase [204]. AhR has been observed in the cells of the seminiferous epithelium, including both Sertoli cells and germ cells, as well as in Leydig cells of the interstitial tissue [206]. In vitro studies of cell cycle dynamics with ongoing TCDD exposure showed inhibited proliferation and G1-phase cell cycle arrest in various cell types, including hepatocytes [188], neuronal cells [207], thymocytes [188], and many kinds of cancer cells [105, 208] through activating AhR [209]. Broadly speaking, it should be noted that the effect of AhR on cell proliferation may vary based on the cell type and the specific phase of the cell cycle [36].

A substantial body of research suggests that the absence of AhR ligand binding or AhR activation may contribute to inflammation [210], apoptosis [119], and oxidative stress in sperm leading to DNA damage [211]. A study revealed that AhR expression in the rat seminiferous tubule is restricted to primary pachytene spermatocytes during stages VII–XI and round spermatids during stages II–XIV of the spermatogenic cycle [212, 213]. In contrast, both AhR and ARNT were found to be expressed in all stages of the seminiferous tubules in human testes [212]. The presence of AhR in sperm has suggested a mechanism by which environmental dioxins, polycyclic aromatic hydrocarbons, and polyhalogenated biphenyls could directly affect sperm function [214]. Mice deficient in AhR show decreased male fertility, sperm count, and weights of seminal vesicles and dorsolateral prostate [119]. Recent reports have also identified AhR immunoreactivity in the Sertoli cells of both rat and human testes [101]. Additionally, AhR signaling is needed to induce the expression of indoleamine 2,3-dioxygenase. Several studies have shown that this enzyme initiates the

pathway of tryptophan catabolism [215, 216]. Furthermore, a deficiency in indoleamine 2,3-dioxygenase has been associated with significant increases in pro-inflammatory markers and the number and percentage of morphologically abnormal sperm [217, 218].

The role of AhR agonists in spermatogenesis

Effects of cigarette smoking and benzo-α-pyrene exposure

The decline in sperm counts and motility, along with abnormal sperm morphology, are among the negative consequences linked to cigarette smoking, which contains Benzo-α-pyrene [158]. This compound serves as an AhR agonist and can harm human health by causing DNA adduct formation and apoptosis in seminiferous tubules [219]. Furthermore, co-culture experiments involving human sperm and benzo-α-pyrene have demonstrated premature acrosome reactions and accelerated hyperactivation, both of which result in dysmorphic sperm and decreased sperm counts in exposed men [220]. Numerous studies have illustrated the destructive impact of Benzo-α-pyrene on sperm motility, suggesting alterations in mitochondrial function, the up-regulation of pro-apoptotic genes at the mitochondrial level, and DNA damage [221]. Similarly, wild-type mice exposed daily to Benzo-α-pyrene showed lower sperm counts and subfertility, and the repercussions are seen in subsequent generations [222]. Metabolically activated Benzo-α-pyrene leads to an increase in ROS generation, inducing oxidative stress, amplified lipid peroxidation, and the activation of caspases and endonucleases [159]. Moreover, the toxic effects of Benzo-α-pyrene are highlighted in in vitro and in vivo studies, depicting p53-mediated male germ cell apoptosis [223]. This process involves the activation of caspases 3, 6, 8, and 9, modification of Bcl-2, modulation of the Fas/FasL system, and activation of MAPKs (ERK 1/2, JNK 1/2, P38 MAPK) which contribute to p53 phosphorylation [158]. Interestingly, studies suggest a negative connection between p53 and AhR activity, implying a potential counteracting role of AhR against p53 activity [224]. Exposure to Benzo-α-pyrene involves AhR activation, nuclear translocation, DNA binding, and the subsequent decrease in the transcriptional activation of CYP1 A1 in various tissue systems [225]. Experimental studies have shown that curcumin and resveratrol, which function as AhR antagonists, can effectively shield against Benzo-α-pyrene-induced testicular germ cell apoptosis [226]. This protective effect corresponds to reduced protein and mRNA expression of CYP1 A1, diminished total AhR levels, and inhibited nuclear translocation of AhR [11, 158, 159, 227].

Activation of MAPK pathways and glucose uptake

Recent empirical evidence robustly supports the involvement of the JNK signaling pathway in maintaining blood-testes barrier function and facilitating germ cell migration. Studies have shown that the activation of the JNK signaling pathway mitigates the disruptive effects of $CdCl_2$ on the blood-testes barrier in adult rats [228, 229]. The ERK signaling pathway plays a direct regulatory role in apoptosis, mitosis, and the progression of germ cell meiosis [230]. Furthermore, the meiosis of spermatocytes depends on the activation of the ERK signaling pathway, as demonstrated in co-culture experiments involving stem cells and pachytene spermatocytes [122].

Curcumin and resveratrol, which act through AhR, initiate the activation of ERK, p38 MAPK, and JNK pathways via the AhR pathway [158, 231–234]. The activation of the p38 MAPK signaling pathway correlates with an elevation in GLUT1 mRNA levels, promoting glucose uptake. Importantly, most genes associated with the MAPK pathway are present in immature rat stem cells. The p38 MAPK signaling pathway is pivotal in promoting JAM-B transcription in response to interleukin-1α stimulation in these cells. Additionally, both the p38 MAPK and ERK signaling pathways play a role in regulating cell junctions [235]. Resveratrol administration to male rats increases the percentages of normal sperm morphology and enhances acrosomal integrity as well as testicular parenchyma features through *Dnah1* mRNA regulation [90].

Environmental impacts of AhR on the male reproductive system

Dioxin or TCDD, a well-established environmental contaminant, is associated with reproductive defects (such as endometriosis, teratogenesis, abortion, and diminished fertility) and endocrine disruption, affecting luteal and follicular steroidogenesis [236]. It is believed that the toxic effects of TCDD are primarily mediated through its ability to activate AhR [237]. Additionally, studies have proven that mice lacking a functioning AhR are resistant to dioxin toxicity [69]. Recent studies suggest a role for oxidative stress, induced by AhR-mediated production of reactive oxygen, in dioxin toxicity [157, 238]. Dioxin-induced production of mitochondrial reactive oxygen species in the testis and other tissues and organs has also been reported [239]. Moreover, dioxin can interfere with endocrine functions during development and adulthood, due to the AhR pathway's crosstalk with several other signaling pathways, including the ER, retinoblastoma protein, hypoxia, NFκB, and TGF-β [240].

Diesel exhaust particles are known to increase serum concentrations of testosterone and the weight of the accessory glands in rats [241, 242]. These particles

contain polycyclic aromatic hydrocarbons that activate AhR and decrease sperm production. Additionally, studies have demonstrated a decrease in the number of sperm and Sertoli cells in mature rats exposed to diesel exhaust particles [150]. The effects of diesel exhaust on spermatids in the testis and epididymis are dependent on AhR [121, 243].

A recent study found that long-term exposure of Zebra fish to an AhR agonist, known as nuburon, led to reproductive toxicity, which was apparent through a decrease in the number of sperm and an increase in oxidative stress levels due to the hyperactivity of the AhR pathway [3]. Moreover, exposing mice to chloro-choline chloride, a plant growth enhancer, could cause environmental concerns through an increased incidence of reproductive toxicity. This toxicity arises from the activation of the AhR/PERK axis, which subsequently leads to poor semen quality and degenerated testicular tissue [4]. However, some environmental pollutants, such as tris(2,3-dibromopropyl) iso-cyanurate, can trigger CYP19a1 toxicity directly via the estrogenic receptor in an AhR-independent mechanism, as revealed in an investigation run on a mouse-spermatogenic cell line [5].

Phthalate-induced male reproductive toxicity

Phthalates are used extensively to enhance the durability of plastics. Studies have shown that Di(2-ethylhexyl) phthalate (DEHP) can cause male reproductive toxicity [244]. This toxicity involves effects on spermatogenesis, disrupting self-renewal, meiosis, and spermatogonia activities [245]. Moreover, phthalates may inhibit testosterone synthesis by impacting the gonadal axis, thereby reducing the quality and quantity of sperm and leading to reproductive disorders [246]. A previous study suggested that phthalates caused DNA damage and apoptosis in sperm, affecting sperm density, vitality, and progressive motility. This decrease in sperm quality, including DNA damage and impaired motility, has been linked to testicular spermatogenesis disorders [247, 248]. Additionally, phthalates increase the expression of CYP1 A1, suggesting AhR pathway activation, which has a variety of effects on different cell functions [249, 250]. Remarkably, phthalate treatment seems to promote the nuclear accumulation of AhR and ARNT, both localizing to the spermatogenic cell nucleus. Interestingly, as the downstream gene targets of the AhR/ARNT signaling system, the levels of CYP1 A1, CYP1 A2, and CYP1B1 were significantly increased following phthalate exposure [165]. Phthalates also seem to induce impairment of blood-testis barrier integrity, which is crucial for normal spermatogenesis [251].

Resveratrol as an AhR antagonist

Resveratrol is a phytochemical present in peanuts, grapes, blueberries, rhubarb, and wine, possessing cytoprotective and antioxidant properties. It functions as an antagonist of the AhR, with one of its mechanisms involving the inhibition of AhR expression [160, 252]. Moreover, resveratrol obstructs the activation of CYP1 A1 and CYP1B1, and this action is associated with a decrease in ROS production [253]. The protective effect of resveratrol on ROS generation is highly significant because peroxidation of polyunsaturated fatty acids can result in lowered membrane fluidity and reduced activity of membrane enzymes and ion channels, potentially endangering sperm motility [254]. Researchers have detailed the mechanism behind resveratrol's actions on AhR, emphasizing its capability to restore the reduction in ERK and p38 MAPK phosphorylation prompted by AhR's ligand agonists [158, 231]. Resveratrol defends cells from DNA damage and apoptosis by moderating the anti- and pro-apoptotic mediators, thus enhancing the antioxidant status [222]. Resveratrol inhibits the enzymatic activity of various cytochrome P450 s and deters their transcription through the antagonism of AhR, implying that resveratrol might lessen cells' cancer-causing exposure, including TCDD [159, 222].

Lycopene supplementation alleviates male infertility

Lycopene is a carotenoid antioxidant located in plants, such as tomatoes. Lycopene supplementation studies in humans and animals have demonstrated potential in alleviating male infertility where the sperm count, and viability increased with Lycopene treatment [255]. Furthermore, Lycopene can abate testicular toxicity, thus offsetting the harmful effects of pollution by managing the CYP450 s homeostasis and the AhR/ARNT signaling system [245]. Studies have shown that administering Lycopene to rats mitigated nearly all testicular structural damage, which included desquamative germinal cells and the slowing of spermatogenesis [251, 256, 257]. Current evidence suggests that lycopene functions as an *antagonist* (or at least an inhibitor) of AhR. Additionally, Lycopene precipitated a substantial decrease in the nuclear accumulation of AhR and ARNT, while their downstream target genes, inhibitors of CYP1 enzymes (CYP1 A1, CYP1 A2, and CYP1B1) were significantly reduced to normal levels. Concurrently, the values of sperm motility, number, and density exhibited an increase [56, 258].

Curcumin supplementation alleviates male infertility

Curcumin is a naturally occurring plant polyphenol found in the ancient Indian spice Turmeric, boasting various beneficial properties. It is known for its antioxidative and anti-inflammatory activity [168, 259]. It

has been reported that curcumin acts as both an agonist and antagonist for the AhR depending on the context of exposure [81, 259]. Without strong ligands like dioxin, curcumin mildly stimulate AhR, effectively behaving as a weak agonist by upregulating certain AhR-responsive genes [81]. Conversely, when potent ligands are present or when the cellular environment includes heightened AhR sensitivity, curcumin frequently serves as an antagonist by blocking ligand binding, promoting AhR degradation, or altering co-factor interactions in a way that diminishes AhR-driven gene expression [169, 259]. A few studies indicate that curcumin can prevent testicular germ cell apoptosis under various stressful conditions [260]. Curcumin enhances resveratrol's effectiveness, and together, they regulate p53 phosphorylation specifically at ser 15 involving MAPKs [159]. Curcumin can also mitigate oxidative stress [261] and inflammation, which are two major contributors to male infertility [260].

The affinity of selected AhR ligands

Table 2 provides an overview of the relative binding affinity of various AhR ligands, indicating whether each ligand exhibits high or low affinity. This summary, based on findings from several studies, highlights that potent agonists such as TCDD and FICZ bind with high affinity. In contrast, other compounds—like benzo[a]pyrene, DEHP, and several dietary modulators (resveratrol and curcumin)—generally display lower affinity.

Epigenetic modifications and transgenerational effects

Epigenetic landscape changes induced by AhR activation

Transgenerational inheritance refers to the transfer of traits or characteristics from one generation to the next, not through alterations in DNA sequences, but rather via modifications of the epigenome. Environmental factors can trigger these modifications and potentially influence the phenotypes of the progeny. Several studies suggest that environmental stimuli can modify parental traits, thus influencing the phenotypes of offspring via gametic epigenetic inheritance. As a result, the role of epigenetic factors and their heritability merit careful consideration in the context of disease risk assessment [266, 267]. The AhR plays a significant role in influencing the epigenetic landscape, particularly regarding transgenerational effects resulting from chemical exposures. Research indicates that AhR activation alters DNA methylation patterns and gene expression, which can affect phenotypic outcomes across generations [268]. In zebrafish exposed to AhR agonists such as benzo-α-pyrene and 7,12-dimethylbenz(a)anthracene, changes in DNA methylation and gene expression have been discovered, suggesting a potential role of AhR-mediated epigenetic modifications in transgenerational effects [269]. Hence, the observed phenotypic alterations in AhR lineage zebrafish raise questions about the contribution of epigenetic changes in the AhR-ARNT signaling regulation to reproductive and skeletal phenotypes. Understanding the persistence and reversibility of these effects is vital for a comprehensive assessment of the impact of AhR activation on transgenerational outcomes [270–272]. Furthermore, it has been demonstrated that AhR activation can modulate DNA methylation patterns in specific genomic regions, impacting the expression of genes involved in various cellular processes [273]. Additionally, histone modifications, such as acetylation and methylation, may be influenced by AhR signaling, further contributing to the regulation of gene expression [273].

Table 2 Relative binding affinity of selected AhR ligands

Ligand	Role	Affinity	Reference
TCDD	Agonist	High	[28, 195]
Benzo[a]pyrene	Agonist	Low	[195]
FICZ	Agonist	High	[195]
DEHP (Phthalate)	Agonist/Modulator	Low	[35]
Resveratrol	Antagonist	Low	[12, 29, 107]
Curcumin	Mixed (Agonist/Antagonist)	Low	[26, 81]
Lycopene	Antagonist/Modulator	Low	[56, 256, 262]
Galangin	Partial Agonist/Antagonist	Low	[154, 263]
α-Naphthoflavone	Antagonist/Partial Agonist	Low	[90, 107, 264, 265]

Transgenerational inheritance of AhR-induced reproductive alterations

Some studies suggest that environmental cues can induce parental changes and affect the phenotypes of offspring through gametic epigenetic inheritance. As a result, epigenetic factors and their heritability should be considered during disease risk assessment. One intriguing aspect of AhR signaling is its potential to induce transgenerational effects, which refer to the transmission of traits or alterations in phenotype across generations, without direct exposure to the environmental stimuli. Research suggests that AhR activation could lead to reproductive changes that can be passed on to following generations [269, 270, 274, 275].

AhR-mediated epigenetic dysregulation and male fertility

Several factors seem to contribute to the outcome of gene transcriptional regulation by AhR, such as the nature of the ligand and its further metabolism by AhR-induced enzymes, the local tissue microenvironment, and the

presence of co-regulators or specific transcription factors in cells. Studies have suggested that AhR activations may lead to epigenetic dysregulation in the male reproductive system, impacting the development and function of sperm [55, 267, 268, 276]. Epigenetic modifications driven by AhR signaling in the male germline can affect the expression of genes involved in spermatogenesis, sperm motility, and fertilization. Understanding these molecular shifts is crucial for discerning the connections between environmental exposures, AhR activation, and male fertility outcomes [268, 277, 278].

In summary, the AhR significantly impacts spermatogenesis, hormonal regulation, and reproductive function, asserting its importance as a regulator of male reproductive health. It underlines its role in male fertility by directing spermiogenesis and ensuring the completion of spermiation. AhR's influence on both reproductive and endocrine processes is demonstrated through its interaction with steroid hormone receptors, particularly estrogen receptors. Male reproductive function can be compromised by environmental chemicals or factors such as phthalates, benzo-a-pyrene, dioxins, and cigarette smoke, through AhR activation. This may subsequently lead to sperm abnormalities and infertility. The complex relationship between AhR and the hypothalamic-pituitary–gonadal axis emphasizes its regulatory role in hormonal and reproductive processes. AhR activation, which can influence reproductive outcomes, may also affect estrogen signaling and modulate gonadotropin surges. Furthermore, AhR-mediated epigenetic modifications may affect gene expression in the male germline, potentially impacting sperm development and fertility.

Most studies examine the effects of xenobiotic AhR ligands such as TCDD are based on animal or in vitro studies with cell lines. There are few epidemiological studies involving people accidentally exposed to xenobiotics. Therefore, more human studies are crucial to verify the effects of environmental AhR ligands on the male reproductive system. Currently, there are no effective treatments for reversing the toxic effects of environmental contaminants like dioxins on the male reproductive system.

Interestingly, dietary AhR ligands or antagonists, including lycopene, resveratrol, and curcumin, may offer some protection against male reproductive toxicity caused by environmental pollutants. Their potential ability to reduce oxidative stress and AhR activation suggests a possible treatment path for enhancing male reproductive health (Graphical Abstract).

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12958-025-01401-3.

Supplementary Material 1.

Acknowledgements
Not applicable.

Authors' contributions
Conceptualization, GB, HA, AM, MN, and PN; Investigation, GB, HA, AM, MN, and PN; Writing—original draft preparation, GB and HA; Writing—review and editing, GB, HA, AM, MN and PN; Visualization, GB and AM; Supervision, HA, and PN. Financial support, MN, and PN. All authors have read and agreed to the current version of the manuscript.

Funding
No institutional funds are available.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.
This review article does not have any individual-related identifiable data or images.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 1 November 2024 Accepted: 25 April 2025
Published online: 14 May 2025

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