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Review Article

The Role of Peroxisome Proliferator-Activated Receptors in the Development and Physiology of Gametes and Preimplantation Embryos

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In several species, a family of nuclear receptors, the peroxisome proliferator-activated receptors (PPARs) composed of three isotypes, is expressed in somatic cells and germ cells of the ovary as well as the testis. Invalidation of these receptors in mice or stimulation of these receptors in vivo or in vitro showed that each receptor has physiological roles in the gamete maturation or the embryo development. In addition, synthetic PPARγ ligands are recently used to induce ovulation in women with polycystic ovary disease. These results reveal the positive actions of PPAR in reproduction. On the other hand, xenobiotics molecules (in herbicides, plasticizers, or components of personal care products), capable of activating PPAR, may disrupt normal PPAR functions in the ovary or the testis and have consequences on the quality of the gametes and the embryos. Despite the recent data obtained on the biological actions of PPARs in reproduction, relatively little is known about PPARs in gametes and embryos. This review summarizes the current knowledge on the expression and the function of PPARs as well as their partners, retinoid X receptors (RXRs), in germ cells and preimplantation embryos. The effects of natural and synthetic PPAR ligands will also be discussed from the perspectives of reproductive toxicology and assisted reproductive technology.

1. INTRODUCTION

Peroxisomes are organelles in eukaryotes that remove toxic substances and break down fatty acid. Peroxisome proliferator-activated receptor α (PPARα) was discovered during the search for a compound that increases the proliferation of peroxisomes in mouse liver cells [1]. Subsequently, two additional isotypes, PPARβ (also known as PPARδ) and PPARγ, were discovered. The three PPARs are encoded by different genes. Variants arising from alternative splicing and usage of different promoters have been reported in all three PPARs [2]. Together they form a subfamily within the steroid receptor superfamily. To date, PPARs have been identified in many species, including *Xenopus*, sea squirt, zebrafish, *Aedes aegypti* (yellow fever mosquito), *Anopheles gambiae* (a species complex which contains six vectors of malaria), mouse, rat, hamster, and human (http://www.ensembl.org/index.html).

Since their discovery, a great deal has been learned about PPARα, PPARγ, and, to a less extent, PPARβ/δ. The knowledge has been applied to clinical practice: synthetic PPARα ligands (fibrates) and PPARγ ligands (thiazolidinediones TZD), respectively, are widely used to treat lipid and glucose disorders. In contrast, the use of PPARs to enhance fertility is constrained by our relative meager knowledge regarding PPARs and reproduction. PPARγ activators have recently been used to induce ovulation in women with polycystic ovary disease, a condition of ovulation dysfunction associated with insulin resistance. This review will focus on the roles of PPARs in the development and physiology of gametes and preimplantation embryos. Also included in the discussion are potential impacts of natural or synthetic PPAR ligand on reproduction and the promising benefits of synthetic PPAR ligands in enhancing the success of assisted reproductive technology.

2. PPARs AND RXRs

PPARs, similar to steroid and thyroid hormone receptors, are ligand-activated nuclear transcription factors. Unlike steroid

and thyroid hormone receptors, PPARs were discovered before their functions were fully understood. Over the years, tissue distribution and synthetic ligands, which bind to specific PPAR, helped to elucidate the biological functions of PPARs.

PPARs form heterodimers with another nuclear receptor, retinoid X receptor (RXR). This interaction occurs in the presence and absence of PPAR ligand. The PPAR-RXR complex recruits other cofactors before binding to PPAR responsive element (PPRE) at the promoter regions of PPAR-responsive genes. Besides PPARs, RXR also forms heterodimers with other nuclear receptors. RXR has three isotypes: RXRα, RXRβ, and RXRγ, all of which are activated by 9-*cis*-retinoic acid (but not by all-*trans* retinoic acid) [3]. The 9-*cis*-retinoic acid was originally considered as the endogenous ligand for RXRs in vivo; but recent reports [4, 5] cast considerable doubt that it is the case. Although RXRs exist as three isotypes, they do not confer different functions to PPAR-RXR complexes. The PPAR-RXR complexes are activated by either PPAR or RXR ligand, but simultaneous binding by both ligands elicits more potent activities [6]. A unique feature of PPARβ/δ, not seen in PPARα or PPARγ, is its ability to repress the transcriptional activities of PPARα and PPARγ. This activity is mediated by corepressors recruited by PPARβ/δ [7].

The DNA sequence of PPRE is typically of a direct repeat 1 (DR1) nuclear receptor in that the PPRE DNA sequence consists of two repeats of AGGTCA separated by one nucleotide (AGGTCA N AGGTCA). Detailed analyses of native PPREs show that the consensus PPRE sequence is 5′-AACTAGGNCA A AGGTCA-3′ [6]. The extended 5′ half site, the one imperfect DR1 core, and the adenine as the spacing nucleotide may confer additional selectivity to the binding of PPAR-RXR complex.

3. DISTRIBUTION AND BIOLOGICAL FUNCTIONS OF PPAR

The functions of PPARs can be extrapolated from tissue(s) expressing the specific PPAR isotype or from the functions of genes regulated by specific PPAR. PPARα is expressed most abundantly in brown adipose tissue and liver, followed by the kidney, heart, and skeletal muscle. PPARγ is mainly expressed in adipose tissue and, to a less extent, in the colon, the immune system, and the retina. Both PPARα and PPARγ responsive genes are involved in lipid homeostasis. Therefore, it is not surprising that the main functions of PPARα and PPARγ are in glucose and lipid homeostasis [6, 8].

On the other hand, the ubiquitous distribution of PPARβ/δ (although gut, kidney, and heart express higher levels than other tissues) makes it difficult to associate PPARβ/δ with specific biological function [8]. The multiple functions of PPARβ/δ are revealed by the diverse genes regulated by PPARβ/δ, such as ILK [9], 11 ß hydroxysteroid dehydrogenase II [10], PTEN [9], and 14-3-3ε [11]. It is worth noting that 14-3-3ε functions as a protein chaperone. Therefore, PPARβ/δ is indirectly associated with even more diverse range of functions. Indeed, PPARβ/δ has been implicated in embryo implantation [12], intestinal adenoma [13], colon cancer [14], skin wound healing [15], hair follicle development [16], and cytoprotection [11].

4. PPAR LIGANDS

Natural and synthetic PPAR ligands relevant to this review are listed below. More extensive lists are available in the literature [6, 17].

Unsaturated fatty acids are ligands to all PPARs, with PPARα exhibiting the highest affinity; saturated fatty acids, on the other hand, are not effective PPAR ligands. Eicosanoids derived from arachidonic acid form a unique group of fatty acids that bind to PPARs. They include leukotrienes, hydroxyeicosatetraenoic acids (HETEs) (both are formed via the lipoxygenase pathway), and prostaglandins (PGs) (formed via the cyclooxygenase pathway). Leukotriene B4 and 8(S)-HETE are PPARα ligand; and 15-deoxy-Δ12, 14-PGJ_2 (15d-PGJ_2, a PGD_2 derivative) is a PPARγ ligand. Synthetic PPARα (fibrates) and PPARγ (TZD) ligands are used to lower blood lipid and glucose, respectively. Prostacyclin (PGI_2) is a natural PPARβ/δ ligand, indeed the uterine PGI_2 generated by cyclooxygenase-2 (COX-2) mediates the implantation of embryos via PPARβ/δ [12]. Synthetic PGI_2 analogs, such as iloprost and carbaprostacyclin, may function as PGI_2 receptor agonists or PPARβ/δ ligands. Although iloprost is used as a PGI_2 receptor agonist to treat pulmonary hypertension and peripheral vascular diseases, no PGI_2 analog has been used as a PPARβ/δ ligand clinically. A recent report indicates that retinoic acid, in cells with high fatty acid binding protein 5 to retinoic acid binding protein-II ratio, may function as a natural PPARβ/δ ligand [18]. This finding may have evolutional or developmental significance in germ cell maturation, gamete function, or embryo development. PGI_2 and retinoic acid may provide functional redundancy to ensure PPARβ/δ activation or they may compliment each other to activate PPARβ/δ in a developmental stage-dependent manner based on the ratio of the two binding proteins.

5. PPAR LIGANDS IN THE REPRODUCTIVE TRACT

Zygotes remain in the oviduct after fertilization and develop to morula or early blastocyst stage embryos before entering into the uterus. It is generally accepted that, compared with cultured embryos (derived from fertilized eggs in vitro or flushed from oviducts at earlier developmental stage), in vivo embryos develop better and have less cell death because oviducts protect the embryos and promote their development [19]. The unique environment provided by the oviduct includes oviduct-derived soluble factors and embryo-derived autocrine factors. Both oviducts and embryos are sources of PPAR ligand(s).

Earlier studies show that the oviduct produces abundant PGE_2 and $PGF_2\alpha$, which regulate its motility. We serendipitously discovered that human [20] and mouse [21] oviducts produce other eicosanoids that activate PPARs. PGI_2 (a PPARβ/δ ligand) is the most abundant product, PGD_2 (whose derivative, 15d-PGJ_2, is a PPARγ ligand), and other products derived from the lipoxygenase pathway are

also produced in substantial amounts. PGI_2 synthesis by mouse oviducts is synchronized with estrus cycles (and, thus, the development of preimplantation embryos). Peak PGI_2 synthetic capacity coincides with the window of receptivity, that is, between the eight-cell and morula stages [21, 22].

Recent reports indicate that human [23] and mouse [24, 25] preimplantation embryos express COX isoenzymes and synthesize eicosanoids. PGI_2 is the most abundant metabolite when radio-labeled arachidonic acid is incubated with blastocyst-stage mouse embryos. Other eicosanoids, such as HETEs and PGD_2 are also produced by mouse blastocysts [24].

6. RXR IN GAMETES AND PREIMPLANTATION EMBRYOS

Gametes and preimplantation embryos express RXRs. Whereas RXRγ-null mice are normal [26], RXRα- [27] and RXRβ-null mice [28] have distinctive phenotypes. Gene knockout studies show that spermatogenesis requires RXRβ. Similarly, oocyte development may be modulated by RXR, which is expressed in both granulosa-cumulus cells and oocytes. Finally, the quality of embryo development may be associated with RXR expression.

6.1. RXR in gametes

RXRα and RXRβ are expressed in human cumulus granulosa cells [29] and bovine oocytes [30]. Although the initial reports on RXRα [27] and RXRβ [28] null mice did not include a description of female reproduction (such as follicular development and ovulation), the localization of RXRα and β in the ovary supports their roles in follicular maturation and oocyte function. RXR may regulate oocyte development directly (via modulating steroidogenesis in the granulosa cells) or indirectly (by affecting oocyte gene transcription) [31]. It is likely that female mice with targeted RXR deletion may suffer subfertility.

The male sterility observed in RXRβ-null mice [28] underscores the essential role of RXR (and its functional partner) in spermatogenesis. In mouse testes, retinoic acid receptors (RARs) and RXR are expressed in well-defined cell populations: RARα and RXRβ in Sertoli cells, RARβ, RXRα, and RXRγ in steps 7 and 8 spermatids, and RARγ in spermatogonia. Mouse spermatocytes, however, do not express RARs [32]. Although RARβ, RXRα, and RXRγ are coexpressed in step 7 and 8 spermatids, RARβ may not functionally couple with either RXRα or RXRγ, because RARβ-, RXRγ-, and RARβ/RXRγ-null mice do not display reproductive defects [32]. On the other hand, RXRβ and RARα may form heterodimer and control spermiation in vivo because both are coexpressed in Sertoli cells and invalidation of either gene in mice leads to similar phenotype [32]. RXRβ-null males are sterile due to oligoasthenoteratozoospermia caused by failed spermatid release (from the germinal epithelium) and abnormal sperm acrosomes and tails [27]. In Sertoli cells, the function of RXRβ (coupled with RARα) may involve lipid metabolism or transport, because they progressively accumulate lipids (which are unsaturated triglycerides) in RXRβ-null mice. In older RXRβ-null males, germ cells degenerate completely and seminiferous tubules are filled with lipid vacuoles [27]. RARα homozygous mutant [33] and mice with targeted RARα ablation in Sertoli cells [34] display similar phenotype. Both have testicular degeneration, failed spermiation, epithelial vacuolation, germ cell desquamation, and apoptosis [34]. Although there is no report concerning RXR expression in spermatozoa, it can be inferred that human sperm express RXR because human sperm express PPARγ (which forms functional complex with RXR) and PPARγ ligand enhances their activities [35].

6.2. RXR in preimplantation embryos

The development of preimplantation embryos was not described in the initial reports describing RXRα- [27] and RXRβ- [28] null mice. However, available information in the literature shows that preimplantation embryos express RXRs. Transcripts of RXRα, RXRβ, and RXRγ are expressed in zebrafish embryos at 1.5 hour postfertilization [36]. RXRα, RXRβ, and $RALDH_2$ (one of the two enzymes oxidizing retinol to retinoic acid) are detected in all stages of preimplantation bovine embryos, including blastocysts which express RXRβ protein in the inner cell mass and the trophectoderm [30]. RXRα, β, and γ transcripts in preimplantation bovine embryos are likely of maternal origin because eight-cell stage and earlier embryos have significantly higher RXR levels than later stage embryos [37]. Furthermore, RXRs may be essential for optimal embryo development because "good-quality" embryos express significantly higher levels of RXR transcripts than "bad-quality" embryos [37]. It can be summarized that RXR expression in preimplantation embryos described above is corroborated by the expression of its partner, PPAR (discussed later). Furthermore, RXR (partners with PPAR or RAR) is crucial to normal embryo development because (1) early stage embryos contain high levels of maternal RXR mRNA, and (2) "good-quality" embryos express higher RXR mRNA levels.

7. PPAR IN GAMETES AND PREIMPLANTATION EMBRYOS

Compared with their role in postimplantation embryo development, the roles of PPARs in fertilization, implantation, and embryo development are less well defined. Available information does suggest that gametes and preimplantation embryos express functional PPARs and that PPAR activation optimizes their functions.

7.1. PPAR and gametes

All three PPAR isotypes are expressed in somatic and germ cells of the testis. In rat, PPARα and β/δ are expressed in Leydig cells and Sertoli cells [38]. In human, PPARγ1 message is detected in the testis [39]. In mouse, both PPARα and γ are expressed in Sertoli cells [40], and PPARβ/δ is expressed in spermatids and spermatocytes [41]. The expression of PPARβ/δ in mouse spermatids and spermatocytes is further supported by the expression of *Ssm*, a novel PPARβ/δ

target gene, in mouse testis [42]. The functionality of PPARα in Sertoli cells is confirmed by its nuclear translocation in response to a selective PPARα ligand, Wy-14,643 [40]. These findings suggest that PPARs (in Sertoli cells and Leydig cells) provide an environment for spermatogenesis and may be directly involved in germ cell maturation. PPAR may regulate germ cell maturation in a stage-dependent fashion. In zebrafish, PPARγ is expressed in spermatogonia but not in spermatocytes [43].

PPAR ligand affects spermatogenesis and sperm activities. Di(*n*-butyl) phthalate, a PPAR activator, modulates the expression of genes related to spermatogenesis and steroidogenesis and causes testicular atrophy in rats [44]. In contrast, the capacitation, acrosome reaction, and motility of ejaculated human sperm are enhanced by a treatment with rosiglitazone (a synthetic PPARγ ligand) or 15d-PGJ2 (a natural PPARγ ligand) [35]. Since germ cells express all three PPAR isotypes, the expression and function of two other PPAR isotypes, PPARα and β/δ, in mature spermatozoa warrant further investigation.

In several species including rat, all three PPAR isotypes are detected in the ovary [2]. PPARγ, which has been studied more extensively than the other two isotypes, is detected in the mouse, rat, pig, sheep, cow, and human ovary. PPARγ is expressed strongly in the granulosa cells of rat [2], mouse [41], and sheep [45], as well as in oocytes from cattle [30], zebrafish [43], *Xenopus* [46], and human [47]. PPARγ is detected in different classes of follicles (primary/secondary to preovulatory follicles) and its expression increases with the development of follicles. After the LH surge, PPARγ mRNA expression is downregulated [2]. Activation of PPARγ by natural and synthetic ligands in the granulosa cells appears to regulate the synthesis of steroid hormones. Thus, PPARγ may be indirectly involved in oocyte maturation via the granulosa cells. Indeed, disruption of PPARγ gene in the ovary using *cre/loxP* technology led to female subfertility [48]. On the other hand, PPARs may be directly involved in oocyte maturation. Indeed, it has been reported that rosiglitazone, a synthetic PPARγ ligand, at 100 μM stimulates AMP-activated protein kinase (AMPK) and enhances the meiotic resumption of mouse oocytes [42].

7.2. PPAR and preimplantation embryos

Preimplantation bovine and mouse embryos express PPARγ and PPARβ/δ, respectively. Beginning at two-cell stage and throughout the preimplantation period, bovine embryos express PPARγ. Blastocyst stage bovine embryos express PPARγ in the inner cell mass and the trophectoderm [30]. Mouse embryos express PPARβ/δ detectable by immunohistochemistry at two-cell stage [25] or eight-cell stage [22] and throughout the preimplantation period. Mouse blastocysts also express PPARβ/δ in the inner cell mass and the trophectoderm [22].

Although preimplantation embryo development and implantation were not specifically examined in the initial report regarding PPARβ/δ-null mouse, the report provides a hint of the impacts of PPARβ/δ deficiency [49]. The genotypic distribution of embryos on gestation day 9.5 shows that PPAR$\beta/\delta -/-$ embryos are underrepresented: PPAR$\beta/\delta -/-$ embryos represent 16% (3/19) and 38% (3/8) of embryos from PPAR$\beta/\delta +/-$ x PPAR$\beta/\delta +/-$ and PPAR$\beta/\delta -/-$ x PPAR$\beta/\delta +/-$ mating, respectively. This represents a 36% (i.e., 25% versus 16%) and a 24% (i.e., 50% versus 38%) deviation from the expected Mendelian frequency. Loss of PPAR$\beta/\delta -/-$ embryos prior to gestation day 9.5 may occur at any stage including ovulation, fertilization, preimplantation period, implantation, and postimplantation period up to gestation day 9.5. The results of our study show that PPARβ/δ ablation adversely affects preimplantation embryo development and, consequently, implantation [22]. Compared with wild-type embryos, PPAR$\beta/\delta -/-$ embryos show developmental delay as early as 48 hours after two-cell stage embryos are harvested. The gap widens in the subsequent 48 hours. At 96 hours after the harvest of two-cell embryos, 100% of wild-type embryos have reached or passed the blastocyst stage (versus 65% PPAR$\beta/\delta -/-$ embryos), and 85% of wild-type embryos have undergone hatching or hatched completely (versus 28% PPAR$\beta/\delta -/-$ embryos). Consequently, PPAR$\beta/\delta -/-$ embryos implant less effectively than wild-type embryos (28% versus 44%). We also found that PPAR$\beta/\delta -/-$ embryos have decreased embryonic cell proliferation compared with that observed in wild-type embryos. These results suggest that PPARβ/δ activation via endogenous PPARβ/δ ligand, such as PGI_2 [24] and/or retinoic acid [18], confers the "basal" momentum (including cell proliferation and possibly other functions) to preimplantation embryos and propels them through various stages of development.

In addition to providing a "basal" momentum of embryo development via endogenous PPARβ/δ ligand, PPARβ/δ activation by synthetic ligand further enhances the development and the implantation of cultured embryos. Both L-165041 (a synthetic PPARβ/δ ligand) and iloprost (a stable PGI_2 analog) enhance complete embryo hatching in a concentration-dependent manner [22, 50, 51]. Embryos preconditioned with L-165041 or iloprost show higher implantation rates when transferred to gestational carriers [22, 52]. These results suggest that cultured embryos do not reach their full developmental potential due to insufficient endogenous PPARβ/δ ligands or lack of exogenous PPARβ/δ ligands normally provided by the oviduct. Embryos exposed to PPARβ/δ ligand have increased embryonic cell proliferation compared with controlled embryos [22].

8. PPAR AND REPRODUCTIVE TOXICOLOGY

PPAR activators are found in herbicides, industrial plasticizers (for a brief review see [53]), and personal care products such as hair spray and solvent for perfumes [54]. Di(*n*-butyl) phthalate, a PPARγ activator found in plasticizers and personal care products, may cause male infertility by altering hormones involved in steroidogenesis and spermatogenesis [44]. Other potential PPAR activators posing reproductive toxicology concerns are pharmaceutical agents used to lower lipids and blood glucose. Rosiglitazone (a TZD for diabetes) may activate PPARγ ligand and enhance sperm activities in men [35] or, depending on its concentration, may enhance

meiosis resumption of oocytes or induce oocyte degeneration in women [55]. Nonsteroidal anti-inflammatory drugs, such as Motrin, which blocks PG synthesis, pose reproductive hazards through a different mechanism. Decreased PG (such as PGI_2) production may adversely affect embryo development and implantation.

On the other hand, PPARs may be exploited to enhance the success of assisted reproductive technology. The fertilization potentials of human sperm in in vitro fertilization (IVF) or other assisted reproductive technologies, such as artificial insemination, may be enhanced by incubating sperm with synthetic PPARγ ligands. The development and implantation of IVF embryos may be augmented by supplementing culture media with PGI_2 analogs, synthetic PPARβ/δ ligand, or retinoic acid. However, potential long-term adverse effects are unknown. Large-scale clinical trials of sufficient power are needed to validate the benefits and to assess the harms.

9. CONCLUSION

The literature on PPARs in gametes and preimplantation embryos is relatively limited. Nonetheless, the consensus is that PPAR serves to optimize gamete function and embryo development. Further studies are needed to shed more light on the physiological roles of PPARs in reproduction. The knowledge gained will help us avoid potential reproductive hazards and augment the success of assisted reproductive technologies.

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