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*Current Pharmaceutical Design*, 2013, *19*, 000-000 1

# The Biology of the Peroxisome Proliferator-activated Receptor System in the Female Reproductive Tract

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**Abstract:** Fuel sensors such as glucose, insulin or leptin, are known to be directly involved in the regulation of fertility at each level of the hypothalamic-pituitary-gonadal axis. The discovery of the peroxisome proliferator-activated receptor (PPAR) family of transcription factors has revealed the link between lipid/glucose availability and long-term metabolic adaptation. By binding to specific regions of DNA in heterodimers with the retinoid X receptors (RXRs), the members of the PPAR family (α, β/δ, ϒ) are able to regulate the gene expressions of several key regulators of energy homeostasis including several glucose regulators (glucose transporters, insulin receptor, substrate insulin receptor, etc), and also metabolic and endocrine pathways like lipogenesis, steroidogenesis, ovulation, oocyte maturation, maintenance of the corpus luteum, nitric oxide system, several proteases and plasminogen activator among others. All the three PPAR isoforms are expressed in different tissues of the female reproductive tract and regulate gametogenesis, ovulation, corpus luteum regression and the implantation process among others. The present review discusses the mechanisms involved in PPAR activation focusing on endogenous and synthetic ligands of PPAR not only in physiological but also in pathological conditions (such as polycystic ovary syndrome, pathologies of implantation process, chronic anovulation, etc).

**Keywords:** Peroxisome Proliferator-activated Receptor (PPAR), female reproductive tract, infertility, fuel sensors, insulin resistance, polycystic ovary syndrome, prostaglandins, ovary, uterus.

## 1. INTRODUCTION

Living organisms have the capacity to adapt their metabolisms to the nutritional environment. Metabolic pathways of glucose and fatty acids, the main energy substrates, have developed strategic mechanisms depending on the tissues [1, 2, 3]. These pathways require a tight regulation which involves not only rapid modulation of the activity of specific proteins such as enzymes or transporters but also longer-term changes in their quality. This can be achieved by regulating their transcription rate through specific transcription factors [1]. The peroxisome proliferator-activated receptors (PPARs) belong to the nuclear receptor superfamily, many of which are responsible for the link between the lipid/glucose availability and the long-term metabolic adaptation. PPARs have the classic domain structure of other nuclear receptors (such as steroid or thyroid hormone receptors) [4]. They have a ligand-independent transactivation domain (AF-1) and a DNA-binding domain (DBD) in the NH2-terminal region and a ligand and dimerization domain (LBD-Dim) and a ligand-dependent activation domain (AF-2) at the COOH-terminus [4] (Fig. **1**).

PPARs bind to DNA in specific sites with the sequence AGGTCANAGGTA as obligate heterodimers with the 9-cis-retinoic acid receptor (RXR) (Fig. **2**). In contrast with other nuclear receptors (as steroid receptors), the PPAR/RXR complex can be activated by the ligand of each receptor and simultaneous binding of both ligands is more efficient.

The PPAR family is composed of PPAR α, β/δ and ϒ. PPARα was the first to be discovered during the search for a compound that increases the proliferation of peroxisomes (organelles in eukaryotes that remove toxic substances and break down fatty acids) in mouse liver cells [1]. The three PPARs are encoded by different genes and variants arising from alternative splicing and usage of different promoters have been reported in all three PPARs [4]. PPARs have been identified in many species including Xenopus, sea squirt, zebrafish, *Aedes aegypti*, *Anopheles gambiae*, mouse, rat, hamster and human [5].

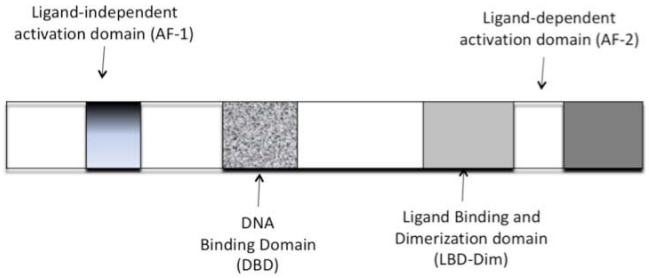


**Fig. (1).** General structure of PPARs.

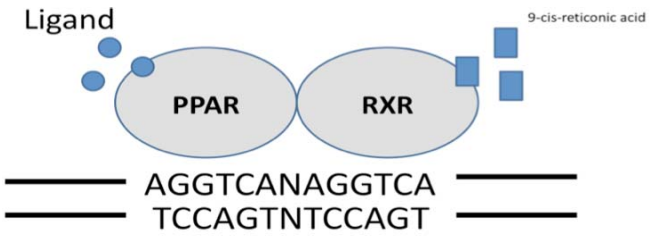


**Fig. (2).** Mechanism of action of PPARs.

### Localization and Biological Functions of PPARs

The functions of PPARs depend on tissue localization. PPARα is mostly expressed in brown adipose tissue and liver, kidney, heart and skeletal muscle [5]. The ubiquitous distribution of PPAR β/δ more highly expressed in gut, kidney and heart makes it difficult to associate PPAR β/δ with specific biological functions [6]. PPAR β/δ has been implicated in embryo implantation [7], intestinal ade-

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1381-6128/13 $58.00+.00 

noma [8], colon cancer [9], skin wound healing [10], hair follicle development [11] and cytoprotection [12]. PPARϒ is mainly expressed in adipose tissue and the retina and both PPARα and PPARϒ are involved in lipid homeostasis [13], thus, the main functions of PPARα and PPARϒ are related to glucose and lipid homeostasis [6, 13].

## PPAR Ligands

A large number of compounds including phospholipids, eicosanoids and n-3 and n-6 fatty acids (FAs) act as endogenous PPAR ligands. Some ligands are specific for each PPAR subtype, while other ligands activate more than one subtype [4]. PPARα ligands include unsaturated FAs, saturated FAs, leukotriene B4 and 8-hydroxyeicosatetraenoic acid (HETE); PPARβ/δ ligands include unsaturated FAs, saturated FAs and very low density lipoprotein (VLDLs) components and PPARϒ ligands include unsaturated FAs, oxidized and nitrated FAs, 15-Deoxy-Δ12,14-prostaglandin J2 (15d-PGJ2), 15-HETE, 9- hydroxyoctadecadienoic acid (HODE), 13-HODE and oxidized low-density lipoprotein (oxLDLs) components [4].

A possible cause of the difference in ligand-specificity could be explained by differences in the binding domain structure of each PPARs [14]. Moreover, these ligands act in different cells or tissues enriched in PPARs and bind to PPARs and coregulators (coactivators or corepressors) of transcription [15, 16]. The analysis of each PPAR ligand is very difficult given their anatomic and diverse distribution and the combinations in which they occur depend on physiological metabolism and pathophysiological conditions (e.g. diabetes, cancer, and atherosclerosis). Thus, the clarification of the action of each individual ligand is a pending task.

On the other hand, a wide range of synthetic ligands is available. These include non-steroidal anti-inflammatory drugs (NSAIDs), fibrates (used to treat dyslipidemia), the thiazoldinediones (TZDs), rosiglitazones, pioglitazones, troglitazones and ciglitazones (used to treat diabetes) and unexpected activators like herbicides and industrial plasticizers. A new class of drugs has been developed to act over either two or three PPAR subtypes, called dual agonists and pan agonists respectively. PPARα/ϒ agonists (naveglitazar, netoglitazone, muraglitazar, ragaglitazar, tesaglitazar, imiglitazar, MK 767, LY 929 and LSN862) produce synergistic anti diabetic and cardio protective effects [17]. PPARα/β and PPARϒ/β dual agonists are currently under process [18-20]. Bezafibrate is a lipid-lowering fibric acid derivative and is a tested pan PPARα/β/ϒ agonist [21-23]. The side effects observed in all synthetic compounds are still a problem to solve and research programs are seeking an ideal synthetic compound having all the beneficial effects with no adverse consequences (Table **I**).

## PPARs in the Reproductive Functions

### *Hypothalamus and Pituitary Gland*

In reproductive tissues, PPARϒ is expressed in the pituitary gland of mice and sheep [24, 25] and in the rat hypothalamus [26]. It has been described that PPARϒ has antiproliferative effects in pituitary cells [24]. In the pituitary gland, PPARϒ expression decreases about 54% after 24 h of restricted food intake [26]. In the human hypothalamus, the PPARϒ ligand PGJ2 plays a role in the regulation of temperature [25], but PGJ2 has not any effect on reproductive functions at this level of signaling. In spite of the presence of PPARϒ system in the hypothalamic-pituitary axis, their roles in the reproductive functions remain unknown [27]. In a recent review, Yang *et al*. [27] discussed these points and reported that TZD treatment failed to modulate hormonal secretion *in vitro* from both ovine pituitary cells and a murine gonadotropic pituitary tumor cell line.

**Table I. Endogenous and synthetic ligands of PPARs.**

| **Endogenous ligands** [4] | **Nature of agonist** |
|---|---|
| Unsaturated FAs | PPARα, PPARβ, PPARγ |
| Saturated FAs | PPARα, PPARβ |
| Leukotriene B4 | PPARα |
| 8-HETE | PPARα |
| VLDLs components | PPARβ |
| Oxidized and nitrated FAs | PPARγ |
| 15d-PGJ2 | PPARγ |
| 15-HETE | PPARγ |
| 9-HODE | PPARγ |
| 13-HODE | PPARγ |
| OxLDLs components | PPARγ |
| **Synthetic ligands** | **Nature of agonist** |
| NSAIDs | PPARα, PPARβ, PPARγ |
| Fibrates | PPARα, PPARγ |
| TZDs | PPARγ |
| Herbicides | PPARγ |
| Industrial Plasticizers | PPARα, PPARγ |
| Dual agonists [17-20] | |
| Naveglitazar | PPARα/γ |
| Netoglitazone | PPARα/γ |
| Muraglitazar | PPARα/γ |
| Ragaglitazar | PPARα/γ |
| Tesaglitazar | PPARα/γ |
| Imiglitazar | PPARα/γ |
| MK 767 | PPARα/γ |
| LY 929 | PPARα/γ |
| LSN862 | PPARα/γ |
| Phenylpropanoic acids | PPARα/β |
| Propanoic acid derivatives | PPARβ/γ |
| Pan agonists [21-23] | |
| Bezafibrate | PPARα/β/γ |

FA: fatty acids, HETE: hydroxyeicosatetraenoic acid, VLDLs: very low density lipoprotein, PGJ2: 15-Deoxy-Δ12,14-prostaglandin J2, HODE: hydroxyoctadecadienoic acid, oxLDLs: oxidized low-density lipoproteins, NSAIDs: non-steroidal anti-inflammatory drugs, TZDs: thiazolidinediones

### *Placenta and Endometrium*

After fertilization and the development to morula or early blastocyst stage, zygotes remain in the oviduct. It seems that by this mechanism oviduct-derived soluble factors protect embryo development. Both, oviducts and embryos are sources of PPAR ligands [29-32].

PPARϒ is essential for the attachment of embryos to the endometrium and the development of the placenta [27, 33], thus contributing to the maternal-fetal transfer of oxygen and nutrients that allow for prenatal growth [34]. In human placenta, PPARϒ is expressed in early and term villous trophoblasts and in extravillous trophoblasts in first-trimester [27, 35], in mouse placenta by day 8.5 of embryo development [27, 36] and by day 11 in rat placenta [27, 37]. In mice, PPARϒ is expressed in spongiotrophoblasts and in the vascular labyrinth that forms the interface between maternal and fetal circulation [27, 37].

Cytokines are essential in modulating endometrial tissue during implantation. It has been reported that interferon gamma (IFNϒ) and interleukin 6 (IL-6) modulate gene expression of PPARs in porcine endometrium [38] and that this mechanism is sensitive to the reproductive status of animals [38]. In contrast, McKinnon *et al.*

[39] demonstrated that thiazolidinediones decrease the proinflammatory cytokines IL-6 and IL-8 in endometrial stromal cells via a PPARϒ-independent mechanism [39].

PPARϒ also modulates genes encoding COX-2 in the endometrium of mice [40] and COX-2 and NOS in human cardiac myocytes and in human prostate cells [41]. In pregnancy, PPAR β/δ mediates the fundamental role of COX-2 derived prostaglandin I2 (prostacyclin, PGI2) [27]. COX-2 knockout female mice displayed decreased fertility due to deficient both blastocyte implantation and decidualization [7, 42]. Moreover, treatment of these mice with a PGI2 analogue, carboprostacyclin or the selective PPAR β/δ agonist L-165041 restores implantation [7]. Therefore, PGI2 is the most abundant PG at implantation site where PPAR β/δ and COX-2 localize and are strongly up-regulated in a similar manner during pregnancy [7].

***Ovary***

In ovarian tissue, PPARα and PPAR β/δ isoforms are expressed primarily in the theca and stromal tissues; whereas the deletion of PPARα has no effect on fertility in mice, the deletion of

PPAR β/δ and PPARϒ does have this effect [43-45]. In the ovaries of ruminants and rodents, PPARϒ is mainly expressed in granulosa cells and less strongly in theca cells and corpus luteum [46]. PPARϒ is expressed in early ovarian follicles modulating the development of primary/secondary follicles and decreasing after the LH surge [47].

The molecular mechanisms of PPARs in the ovarian functions are not fully understood. It has been reported that PPARϒ regulates the expression of genes required for follicular development, ovulation, oocyte maturation and maintenance of the corpus luteum [28]. It has also been reported that PPARϒ mediates both steroidogenesis and apoptosis of antral follicles from pubertal rats [48, 49].

Previous works have shown that genes encoding cyclooxygenase-2 (COX-2) and nitric oxide synthase (NOS) are implicated in female reproductive functions, as ovulation, oocyte meiotic maturation and corpus luteum development [50, 51].

## PPARs and Pathological Status

***Hypothalamus and Pituitary***

The role of the PPAR system in the pituitary gland is not fully understood. The administration of PPARγ ligands inhibits the development of pituitary adenomas in mice and humans by an antiproliferative action [24]. In contrast, Froment *et al* [46] found that the *in vitro* treatment of the ovine pituitary with TZDs does not affect prolactin (PRL), growth factor (GH), follicle stimulating hormone (FSH) or luteinizing hormone (LH) production. Despite the presence of 15d-PGJ2, the natural ligand of PPARγ, in the human hypothalamus, its role is still not completely understood [46].

***Placenta and Endometrium***

Maternal undernutrition during pregnancy results in intrauterine growth-restricted fetuses and small placentas. Belkacemi *et al* [52] reported that PPARγ expression is significantly down-regulated in apoptotic zones of undernourished pregnant rats. In agreement with this, placentas from appropriate-gestational age (AGA) and large-for-gestational-age (LGA) infants show nearly 2-fold higher PPARγ expression than those from small-for-gestational-age (SGA) infants [34]. Moreover, placental PPARγ expression has been positively associated with placental and/or fetal weight at birth, particularly within the SGA subpopulation [34]. PPARϒ plays a pivotal role in the progression of a healthy pregnancy and may critically regulate the risk of preeclampsia, the main cause of maternal and perinatal mortality and morbidity [53].

It has been recently reported that the PPAR/RXR pathway contribute to endometrial carcinogenesis by modulating vascular endothelial growth factor (VEGF) secretion [54]. Therefore, hyperandrogenism alters PPARϒ expression in endometrial tissue of mice [40].

In a recent review, Yang *et al*. [27] discussed the relationship between PPARϒ and fertility. The deletion of PPARϒ in granulosa cells reduces fertility [55] and PPARϒ-null embryos died by embryonic day 10 [56] as a result of deficient vascularization of placenta. PPARϒ plays an important role during early pregnancy [27]. Activation of PPARϒ stimulates the differentiation of the placenta characterized by fusion of cytotrophoblasts into syncytiotrophoblasts, a more resistant form to hypoxic injury [27, 56]. As a potent endogenous PPARβ/δ ligand, PGI2 increases vascular permeability [57, 58] and blastocyst hatching [59]. For these reasons, PPARβ/δ-null mice display abnormal vascular development [60] and that giant-cell differentiation of plancentas requires intact PPARβ/δ signaling pathway [27, 59].

***Ovary***

Controversial results have been reported about the role of TZDs in the secretions of steroids in granulosa cells. *In vitro*, TZDs stimulate progesterone and estradiol secretion by rat and ovine granulosa cells [46, 47], bovine lutein cells [50] and porcine theca cells [61], whereas they inhibit the production of progesterone and estradiol production by porcine and human granulosa cells [62, 63]. In agreement with other authors [28] we suggest that the species but specially the status of granulosa cells could modulate the TZD actions on steroidogenesis. Moreover, a direct effect on the activity of steroid enzymes rather than on the promoters of the genes encoding these enzymes has been reported [28]. In addition to the effect of PPARϒ on steroid secretion, TZDs exert an antiproliferative action [46, 64].

The excess of androgens alter the protein and gene expression of PPARϒ. In fact, ovarian tissue from prenatal hyperandrogenized rats has shown the up-regulation of PPARϒ genes which also correlates to the up-regulation of COX-2 genes [49]. These data suggest, that PPARϒ is related to the inflammatory status of the ovarian tissue. In addition, considering that the decrease in PPARϒ after the preovulatory surge of LH is a necessary condition [65, 66], we suggest that the increased PPARϒ production under hyperandrogenism could be one of the causes to avoid the dominant follicle in women with Polycystic Ovary Syndrome (PCOS). The association between PPARϒ and inflammation has also been described in other tissues. Recently Margalit *et al* [67] demonstrated that PPARϒ agonists target aromatase expression via prostaglandin E2 (PGE2) in breast cancer.

Adiponectin is an adipokine that increases sensitivity to insulin and modulates vasodilation [68]. In porcine granulosa cells, adiponectin treatment induces the expressions of genes associated with peri-ovulatory remodeling of ovarian follicles such as those related to COX-2, PGE synthase and VEGF [69]. These genes are also activated by PPARϒ [70].

***Obesity***

Obesity has been recognized as a chronic disease by the National Institutes of Health Consensus [71]. Chronic disruption of the energy balance due to exceeding energy intake causes hypertrophy and hyperplasia of fat cells leading to obesity. Adipose tissue is placed into large depots (subcutaneous and visceral) and small depots (heart, epicedium, large blood vessels, major lymph nodes, adrenal glands, brain, reproductive tissues, etc) [72]. The preadipocyte enters the adipogenesis stage via environmental and gene expression signals. At an early stage of adipogenesis, PPARϒ regulates the expression of adipogenesis related genes thus indirectly modulating adipokines secreted by adipocytes [73]. Adipokines play an important role in glucose and lipid metabolism, immune system, appetite regulation and vascular diseases [73].

PPARα up-regulates the expressions of catabolic enzymes involved in the maintenance of the redox balance during the oxidative

catabolism of fatty acids [74]. Then, PPARα activators, as fibrates, are used in the treatment of hypertriglyceridemia [74].

Plasma concentrations of adiponectin, the hormone responsible for insulin sensitivity and vasodilation, decreased in obese and type 2 diabetic humans [68], whereas the TZD treatment increases the production and plasma concentration of adiponectin [75].

Dyslipidemia is a common feature of both obese and lean women with PCOS [76]. In addition, dyslipidemia is associated with insulin resistance and enhanced cardiovascular risk [77]. For these reasons current diagnostic guidelines of cardiovascular risk of PCOS patients have been carefully studied to search for lipid markers [78]. We have recently demonstrated that prenatally hyperandrogenized female offspring rats have a condition that resembles the polycystic ovary (PCO) [79]. In that context we found that prenatal hyperandrogenism alters the gene expression of ovarian PPARϒ and that alterations in both dyslipidemia and PPARϒ gene expression are higher in the most severe PCO phenotype [79].

## 2. CONCLUSIONS

PPAR is a family of transcription factors that link lipid/glucose availability and long-term metabolic adaptation. The PPAR family is composed of three subtypes: α, β/δ and ϒ which bind to specific regions of DNA in heterodimers with the retinoid X receptors (RXRs) thus, regulating the gene expressions of several key regulators of energy homeostasis. PPARs are distributed to different tissues, including those of the female reproductive tract. By modulating gene expressions, PPARs are able to act on several glucose regulators (glucose transporters, insulin receptor, substrate insulin receptor, etc), as well as lipogenesis, steroidogenesis, ovulation, oocyte maturation, maintenance of the corpus luteum, nitric oxide system but also several proteases and plasminogen activator among others. The three PPAR isoforms are expressed in different tissues of the reproductive female tract and regulate gametogenesis, ovulation, the corpus luteum regression, the implantation process, between others.

In agreement with Yang *et al.* [27], we believe that the modulation of both endogenous and synthetic ligands of PPARs represents an important tool in pathological conditions.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

## ACKNOWLEDGEMENTS

We thank the support of Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) for the support from PIP 185, Agencia Nacional de Investigaciones Científicas y Tecnológicas (ANPCyT) for the support from PICT 71/2010. We thank Marcela Marquez and Enzo Cuba for their technical support in animal care.

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**Received: March 1, 2013** **Accepted: April 3, 2013**