REVIEW

Peroxisome proliferator-activated receptors in reproductive tissues: from gametogenesis to parturition

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Abstract

Peroxisome proliferator-activated receptors (PPAR α , PPAR β/δ and PPAR γ) are a family of nuclear receptors that are activated by binding of natural ligands, such as polyunsaturated fatty acids or by synthetic ligands. Synthetic molecules of the glitazone family, which bind to PPAR γ , are currently used to treat type II diabetes and also to attenuate the secondary clinical symptoms frequently associated with insulin resistance, including polycystic ovary syndrome (PCOS). PPARs are expressed in different compartments of the reproductive system (hypothalamus, pituitary, ovary, uterus and testis). Conservative functions of PPARs in mammalian species could be suggested through several *in vivo* and *in vitro* studies, especially in the ovary and during placental development. Several groups have described a strong expression of PPAR γ in ovarian granulosa cells, and glitazones modulate

granulosa cell proliferation and steroidogenesis *in vitro*. All these recent data raise new questions about the biologic actions of PPARs in reproduction and their use in therapeutic treatments of fertility troubles such as PCOS or endometriosis. In this review, we first describe the roles of PPARs in different compartments of the reproductive axis (from male and female gametogenesis to parturition), with a focus on PPAR γ . Secondly, we discuss the possible molecular mechanisms underlying the effect of glitazones on PCOS. Like other 'insulin sensitizer' molecules, such as metformin, glitazones may in fact act directly on ovarian cells. Finally, we discuss the eventual actions of PPARs as mediators of environmental toxic substances for reproductive function.

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Introduction

PPAR γ is a nuclear receptor of the peroxisome proliferator-activated receptor family, which also includes PPAR α and PPAR β/δ (for review, see Sorensen *et al.* 1998, Desvergne & Wahli 1999). PPAR γ is activated after the binding of natural ligands such as polyunsaturated fatty acids and prostaglandin metabolites. It can also be activated by synthetic ligands such as thiazolidinediones (TZDs), also known as glitazones (rosiglitazone, pioglitazone or troglitazone) (Lehmann *et al.* 1995). The binding of TZDs to their receptors increases insulin sensitivity, and most bind primarily to PPAR γ in adipose cells. TZDs are frequently administered to patients with insulin resistance associated with type II diabetes (for review, see Houseknecht *et al.* 2002, Gurnell *et al.* 2003, Staels & Fruchart 2005).

Since the discovery of PPARs in 1990 (Issemann & Green 1990), numerous functions have been attributed to these receptors. In addition to enhancing insulin sensitivity, PPAR γ has been shown to regulate fat mass and cell proliferation (Debril *et al.* 2001) and to modulate inflammatory reactions. Three PPAR isoforms are expressed in the central nervous system and in the following reproductive tissues: gonads (ovary, testis), uterus, prostate, mammary gland and pituitary gland (Komar *et al.* 2001, Froment *et al.* 2003, Mouihate *et al.* 2004).

Fuel sensors, such as glucose, insulin or leptin, are known to be directly involved in the regulation of fertility at each level of the hypothalamo-pituitary-gonad axis (for review, see Poretsky *et al.* 1999, Froment *et al.* 2001). For example, mice lacking insulin-signaling pathway components, such as insulin receptor substrate 2 (IRS-2)

or insulin receptor, exhibit female and male infertility (Bruning *et al.* 2000, Burks *et al.* 2000). PPAR γ activation modifies the transcription and/or activity of different key regulators of energy homeostasis (Devergne & Wahli 1999), for example stimulation of several glucose regulators (glucose transporters, insulin receptor, IRS, etc.) (for review, see Picard & Auwerx 2002). We can hypothesize that PPAR γ acts also as a fuel sensor in reproductive compartments to inform cells on the energy status. In this case, PPAR γ may be a link between energy metabolism and reproduction, as in polycystic ovary syndrome (PCOS), which is frequently associated with insulin resistance.

Expression and putative roles of PPARs in reproductive tissues

Hypothalamic-pituitary axis

In the last 3 years, several teams have demonstrated PPAR γ expression in the pituitary gland (mouse and sheep) (Heaney *et al.* 2003, Mouihate *et al.* 2004) and in the hypothalamus (rat) (Mouihate *et al.* 2004). PPAR γ has antiproliferative effects in pituitary cells (Heaney *et al.* 2003), and the administration of TZDs inhibits the development of pituitary adenomas in mice and man. Moreover, PPAR γ expression in the pituitary gland may decrease by about 54% after 24 h of restricted food intake (Wiesner *et al.* 2004).

In the human hypothalamus, PPAR γ may play a role in temperature regulation, as its natural ligand is 15d-PGJ2 (15-deoxy- Δ 12,14-prostaglandin J₂), which is secreted into the cerebrospinal fluid (Mouihate *et al.* 2004). Despite its presence in these organs, PPAR γ does not seem to affect reproductive function at this level of signaling. Indeed, *in vitro*, the secretion of ovine pituitary hormones, including PRL (prolactin), GH (growth hormone), FSH (follicle-stimulating hormone) and LH (luteinizing hormone), and LH secretion by murine LbetaT2 gonadotropic pituitary tumor cells do not seem to be affected by TZD treatment (Froment *et al.* 2003).

Testis

In the testis, the three PPAR isoforms are expressed in both somatic and germ cells (Braissant *et al.* 1996, Elbrecht *et al.* 1996, Bhattacharya *et al.* 2005). PPAR α and PPAR β/δ are widely expressed in interstitial Leydig cells and seminiferous tubule cells (Sertoli and germ cells) (Braissant *et al.* 1996, Schultz *et al.* 1999). On the other hand, PPAR γ is thought to be restricted to Sertoli cells (Elbrecht *et al.* 1996, Corton & Lapinskas 2005). However, Thomas *et al.* (2005) recently detected PPAR γ mRNA in germ cells (spermatocytes) (Fig. 1d). The action of PPARs in the testis is unclear, but these receptors

do not seem to play an important role in fertility. Indeed, PPAR α - and PPAR β/δ -null mice are viable and fertile (Lee *et al.* 1995, Peters *et al.* 2000). Xenobiotic ligands of PPAR γ and PPAR α induce the translocation of these receptors to the nucleus of Sertoli cells (Bhattacharya *et al.* 2005). PPAR γ is also more strongly expressed in human testicular cancer cells than in normal testicular tissues. PPAR γ ligands (TZDs or 15d-PGJ2) have antiproliferative effects on testicular cancer cells (Hase *et al.* 2002). In addition, the incubation of testicular tissue with TZDs induces a decrease in the level of mRNA for resistin, which impairs insulin sensitivity and glucose tolerance (Nogueiras *et al.* 2004). The expression of PPAR α is upregulated by FSH (Schultz *et al.* 1999), a key hormone that also stimulates the production of testicular fluid components, protein synthesis and the mobilization of energy sources. PPAR α may play a physiologic role in steroidogenesis (see below, under heading 'PPARs – mediators of endocrine disruptors of environmental origin?') and may influence the fertility of spermatozoa. Indeed, PPAR α regulates the beta-oxidation of lipids and may also regulate the fatty acid composition of phospholipids in germ cells. The lipid composition of spermatozoa is known to modulate their mobility and its viability (Douard *et al.* 2003).

Ovary

Expression and localization (Fig. 1a and b) The PPAR α and PPAR β/δ isoforms are expressed primarily in the theca and stroma tissues. PPAR α deletion has no apparent effect on the fertility of mice, but the deletion of PPAR γ and PPAR β/δ does have this effect (Lee *et al.* 1995, Peters *et al.* 2000, Barak *et al.* 2002). In the ovaries of rodents and ruminants, PPAR γ is expressed strongly in the granulosa cells, and less strongly in the theca cells and corpus luteum (Gasic *et al.* 1998, Komar *et al.* 2001, Froment *et al.* 2003). PPAR γ is detected early in folliculogenesis, at the primary/secondary follicle stage (Komar 2005). PPAR γ expression increases until the large follicle stage (Froment *et al.* 2003, Komar 2005), and decreases after the LH surge (Komar *et al.* 2001) (Fig. 1a and b).

PPAR γ action on steroidogenesis and proliferation during folliculogenesis Several studies have shown that TZDs present contradictory actions on secretion of steroids (inhibition or stimulation of progesterone and estradiol production) in granulosa cells (Fig. 1c).

Thus, TZDs stimulate *in vitro* the secretion of steroids (progesterone and estradiol) by rat and ovine granulosa cells (Komar *et al.* 2001, Froment *et al.* 2003), bovine lutein cells (theca- and granulosa-derived cells) (Lohrke *et al.* 1998) and porcine theca cells (Schoppee *et al.* 2002), whereas they inhibit the secretion of progesterone and

Gonad : testis

Gonad : ovary

Figure 1 Expression of PPAR γ in gonads. (a) PPAR γ is strongly expressed in granulosa cells in primary to preovulatory follicles in the ovary (human, rat, mouse and ewe). (b) PPAR γ expression decreases after ovulation induced by human chorionic gonadotropin (hCG) stimulation. (c) Schematic representation of steps leading to progesterone, estradiol and testosterone production. The names of enzymes involved in steroid synthesis and regulated by TZDs (activity or expression) are underlined. (d) In the testis, PPAR γ is detected primarily in the Sertoli cells, with weak expression in spermatocytes. The names of the cells expressing PPAR γ are underlined.

estradiol by porcine granulosa cells and by human granulosa cells from patients who underwent *in vitro* fertilization (Gasic *et al.* 1998, Mu *et al.* 2000).

The species and the status of the granulosa cell differentiation (follicular phase, before or after the gonadotropin surge) could modulate these actions of TZDs on steroidogenesis. For example, TZDs stimulated progesterone secretion by a mixture of granulosa, theca and stroma human cells obtained from premenopausal/perimenopausal patients without gonadotropin treatment at the time of oophorectomy (Seto-Young *et al.* 2005). However, TZDs inhibited progesterone secretion by human granulosa cells obtained from adult women who underwent *in vitro* fertilization, as stated above (after equine (e) chorionic gonadotropin (CG) and human (h)CG stimulation), or by luteal-granulosa cells obtained from PCOS patients.

These actions of TZDs probably induce more an effect on the activity of steroidogenic enzymes (3- β -hydroxysteroid-dehydrogenase (3- β HSD) and aromatase) than a direct effect of PPAR γ activation on the promoters of the genes encoding these enzymes (Gasic *et al.* 1998, 2001, Mu *et al.* 2000). Indeed, Gasic *et al.* (1998) reported that TZDs 'did not affect messenger RNA concentrations of Cyp11a1 and 3- β HSD by using standard Northern methodology'. On the other hand, in media from porcine granulosa cells, TZD treatment increased the release of pregnenolone, a precursor of progesterone and substrate of 3 β -HSD, whereas it decreased the release of progesterone. These results suggest that TZDs decrease the activity of the 3 β -HSD enzyme. Moreover, no effect on the amount of Cyp11a1 and 3- β HSD proteins in ovine granulosa cells (Froment *et al.* 2003) or of CYP17 protein in porcine theca cells (Shoppee *et al.* 2002) was observed after TZDs treatment. However, in human, granulosa-like tumor KGN cells, the activation of PPAR γ was recently shown to downregulate aromatase gene expression via the NF- κ B pathway (Fan *et al.* 2005).

In addition to the effects of PPAR γ binding on steroid secretion, TZDs decreased the proliferation of sheep granulosa cells (Froment *et al.* 2003), and the viability of rat granulosa cells (Lovekamp-Swan & Chaffin 2005), in association with an increase in the expression and/or stabilization of tumor suppressor p53 (Lovekamp-Swan & Chaffin 2005). However, *in vivo*, PPAR γ expression was not found to be correlated with the atresia status of follicles (atresia is a process leading to follicular growth arrest, mediated by apoptosis) (Komar *et al.* 2001, Froment *et al.* 2003).

PPAR γ action in corpus luteum In cattle, the expression of PPAR γ in corpus luteum increases after ovulation. However, if no fertilization or embryo implantation occurs, the corpus luteum regresses and PPAR γ expression decreases (Lohrke *et al.* 1998, Viergutz *et al.* 2000) (Fig. 2). In chickens, a similar correlation was observed between

the onset of egg laying, and the increase in PPAR γ levels in the ovaries (Sato *et al.* 2004). In mice, the tissue-specific deletion of PPAR γ in the ovaries, epithelial cells and lymphocytes leads to a decrease in fertility (Cui *et al.* 2002). This decrease is not due to changes in ovarian folliculogenesis or ovulation rate. Instead, it results from a decrease in the number of embryos implanted, and this, in turn, probably results from a decrease in progesterone secretion by the corpus luteum (Cui *et al.* 2002). Furthermore, 4 weeks of ciglitazone injection in rats did not modify folliculogenesis, but did increase serum progesterone concentration (Lebovic *et al.* 2004). Thus, PPAR γ seems to play a significant role in fertility control. In particular, this receptor could be responsible for preserving corpus luteum function (i.e. progesterone production to support implantation and gestation) during pregnancy in various species.

Possible molecular mechanisms Molecular mechanisms of PPARs in ovarian functions are not fully understood. Comparisons with other cell models suggest that PPAR γ may regulate the expression of genes required for follicular development, ovulation, oocyte maturation and maintenance of the corpus luteum. For example, the genes encoding cyclooxygenase-2 (COX-2) and nitric oxide synthase (NOS) are implicated in ovulation and oocyte meiotic maturation, as attested by the invalidation of these genes in mice (Lim *et al.* 1997, Jablonka-Shariff *et al.* 1999). PPAR γ downregulates COX-2 and NOS in human cardiac myocytes and in human prostate cells (COX-2) (Mendez & LaPointe 2003). Interestingly, LH surge downregulated expression of PPAR γ in granulosa cells and PPAR γ and PPAR α in ovarian macrophage cells. TZD treatment decreased expression of iNOS (inducible NOS) in ovarian macrophage cells (Minge *et al.* 2006). We can speculate that the diminution of PPAR γ expression after LH preovulatory surge (Banerjee & Komar 2006, Minge *et al.* 2006) may be associated with an increase in NOS and COX-2 activities (i.e. increase in prostaglandin synthesis) prior to ovulation.

In addition, several proteases (matrix metalloprotease-9, plasminogen activator and plasminogen activator inhibitor (Kato *et al.* 1999, Xin *et al.* 1999, Shu *et al.* 2000)), which play a role in the follicular rupture process and help in tissue remodeling (folliculogenesis and corpus luteum formation), are regulated by PPARs.

Moreover, the formation and function of corpus luteum involve angiogenesis, steroidogenesis and secretion of prostaglandins. Several observations described above suggest a potential role of PPAR γ in steroidogenesis and prostaglandin production. Other studies suggest that PPAR γ plays a role in angiogenesis, as by regulating vascular endothelial growth factor (VEGF), secreted by lutein cells. VEGF maintains the corpus luteum function during pregnancy (Kaczmarek *et al.* 2005). Indeed, inhibition of VEGF decreases the degree of vascularization

Figure 2 Role of PPAR γ in favoring implantation. (a) The corpus luteum expresses PPAR γ . Note that PPAR γ expression decreases in the absence of implantation. (b) PPAR γ is expressed in uterine tissue and in the blastocyst. The expression of PPAR γ in luteal cells stimulates progesterone secretion, favoring implantation. PPAR γ in uterine tissue increases placental vascularization.

and the progesterone secretion by corpus luteum (Fraser *et al.* 2000). In a human macrophage model and in human vascular smooth muscle cells, PPAR γ upregulated VEGF (Bamba *et al.* 2000, Yamakawa *et al.* 2000), suggesting that PPAR γ could regulate the function of the corpus luteum (i.e. progesterone secretion) involved in implantation and gestation by several actions.

Do PPARs contribute to pathologic subfertility?

Link between polycystic ovaries and insulin metabolism

The number of patients with insulin resistance has increased over the last decade, and 3–5% of adults in Occidental countries now have type 2 diabetes. Insulin-resistant women present a higher than average risk of developing fertility disorders. One such disorder, polycystic ovary syndrome (PCOS), is the most frequent cause

of female infertility, affecting ~5–10% of adult women (Dunaif 1997). It is associated with insulin resistance in 60% of cases. This condition is characterized by the formation of cysts in the ovaries, chronic absence of ovulation and clinical signs of hyperandrogenism (Dunaif 1997, Deneux & Kuttann 1998). The etiology of this polyfactorial syndrome is unclear, but several endocrine abnormalities, such as increase in insulin and LH levels, have often been observed (Marshall & Eagleson 1999). In particular, high circulating LH levels with no preovulatory surge may lead to excess androgens and contribute to the formation of cystic follicles, as described in the mouse model (Risma *et al.* 1995). A second example is provided by dysregulation of the insulin pathway, rendering theca cells hypersensitive to LH and increasing androgen production (Rosenfield 1999). Mutations in the insulin receptor gene associated with insulin resistance have been described in several cases of PCOS (Dunaif 1999, Jonard & Dewailly 2002).

The treatment of diabetic PCOS patients with insulin sensitizers of various drug families, such as TZDs, metformin and D-chiro-inositol, increases the fertility of these patients (Dunaif *et al.* 1996, Nestler *et al.* 1999, Iuorno & Nestler 2001, Seli & Duleba 2004).

Metformin, a biguanide, has been used for the past 40 years as an oral treatment for type 2 diabetes. Its mechanism of action is based on the stimulation of peripheral glucose uptake and the inhibition of gluconeogenesis in the liver. Recent reports indicate that metformin action involves the activation of AMP-activated protein kinase (AMPK), a regulator of energy metabolism involved in fatty acid and cholesterol metabolism (Zhou *et al.* 2001, Musi *et al.* 2002). Metformin also decreases Cyp17 activity (P450-17-hydroxylase) (Fig. 1c), and consequently circulating androgen levels and the mean duration of the follicular phase (La Marca *et al.* 2000). Interestingly, we recently showed that AMPK is expressed in rat ovary. Its activation decreased 3 β -HSD protein levels and reduced progesterone production in cultured rat granulosa cells (Tosca *et al.* 2005). As with PPAR γ , it is difficult to exclude a possible direct action of metformin on the ovary via AMPK in patients treated for PCOS.

TZDs, such as rosiglitazone and pioglitazone, are used to decrease peripheral insulin resistance, and have the same effects as metformin. In women, TZDs decrease circulating androgen and LH levels indirectly by lowering insulin levels, leading to an increase of the rate of ovulation and the number of successful pregnancies. In contrast, no significant change in body-mass index is observed (Dunaif *et al.* 1996). There is thus a clear connection between ovary function and glucose and insulin metabolism. The molecular mechanisms underlying this link remain to be clarified.

Biologic effects of TZDs in the treatment of polycystic ovaries: a direct or indirect mechanism of action?

As PPAR γ is clearly expressed and active in the ovary, the effects of TZD in PCOS may be accounted for by a direct action on theca and granulosa cells. However, this role of PPAR γ remains hypothetical. Indeed, in PCOS, granulosa cells *in vivo* undergo premature differentiation into luteal cells and display increases in basal sex steroid secretion *in vitro* (Rosenfield 1999). Thus, we may expect to observe a systematically inhibiting effect of the TZDs on steroid secretion *in vitro*, but this is clearly not the case (see above, under the heading 'Expression and localization'). General improvements in insulin sensitivity in the periphery may partly account for the effect of TZDs on ovulation, via an unknown mechanism. Several observations described below are in accord with this indirect action of TZDs in the treatment of PCOS.

First, plasma free fatty acid and/or triglyceride concentrations are high in PCOS patients (Holte *et al.* 1994). Hypothetically, TZDs could redirect the flow of tri-

glycerides to adipose tissue, decreasing plasma free fatty acid and triglyceride concentrations. Indeed, PPAR γ is widely recognized as a major regulator of adipocyte differentiation (Duran-Sandoval *et al.* 2003).

This TZD-induced return to a 'normal metabolic state' may lead to the secretion of normal amounts of GnRH (gonadotropin-releasing hormone) and, consequently, to normal levels of FSH and LH secretion.

Secondly, two ovary-independent mechanisms can lead to a decrease in androgen levels, and may indirectly improve ovarian function.

1. TZD treatment increases SHBG (steroid hormone-binding globulin) levels in serum, leading to a decrease in free circulating androgen levels (Brettenthaler *et al.* 2004).

2. In addition, after long-term treatment, TZDs have a specific effect not seen with metformin: an increase in body fat associated with adipose tissue redistribution, with a decrease in visceral abdominal adipose tissue and an increase in subcutaneous adipose tissue (Larsen *et al.* 2003).

The accumulation of visceral fat deposits has been shown to be associated with high serum androgen concentrations (Bjorntorp 1996). Thus, the decrease in the profound visceral abdominal adipose tissue could help to explain the decrease of testosterone production.

Finally, recent data on insulin-resistant men treated with TZDs support the hypothesis of a regulation of steroid secretion, which is not mainly due to a direct action of TZDs on the gonads. Indeed, in contrast of women, men with type 2 diabetes have low testosterone secretion levels (Pitteloud *et al.* 2005), and the administration of rosiglitazone or pioglitazone to these patients could induce an increase in testosterone levels (Kapoor *et al.* 2005, Patel *et al.* 2005). Interestingly, PPAR γ is not detected in Leydig cells (cells producing androgens), suggesting that the modulation of serum testosterone levels is not due to a direct action of PPAR γ on the gonad.

PPARs – mediators of endocrine disruptors of environmental origin?

PPAR family members also bind to xenobiotic ligands, increasing the size and number of peroxisomes (Corton & Lapinskas 2005). These ligands include industrial chemicals, such as herbicides, oil derivatives and plasticizers, including phthalate esters. Phthalate esters are components of various types of plastic, such as those used to make storage containers, but are also present in perfumes and cosmetics. Many phthalates are toxic in reproductive function. For example, di-(2-ethylhexyl) phthalate (DEHP) causes considerable damage to somatic and germ cells in the testis, leading to a decrease in sperm production and, in some cases, testicular atrophy (Mylchreest *et al.* 1998). A recent study showed that phthalate esters decrease testosterone secretion (Thompson *et al.* 2005) and increase the apoptosis of germ cells in rat testis (Bhattacharya *et al.* 2005). The administration of phthalate

Figure 3 Role of PPAR γ during gestation and parturition. (a) PPAR γ plays a key role in placental maturation (placental vascularization and placental hormone secretion). PPAR γ favors the maintenance of gestation by decreasing COX-2 production, stimulating progesterone secretion and reducing endometrial inflammation. (b) During labor, PPAR γ levels decrease in the fetal membranes and amnion, decreasing the inhibition of prostaglandin production. Prostaglandins are key hormones favoring uterine contraction and cervical dilation.

esters to female rats leads to an increase in the length of the estrous cycle and dysovulation (Davis *et al.* 1994).

Limited experiments have shown that phthalate esters may interfere with reproduction by interacting with PPARs. PPAR α and PPAR γ are responsive to DEHP *in vitro* and are translocated to the nucleus in primary Sertoli cells after the incubation of these cells with phthalate esters (Dufour *et al.* 2003, Bhattacharya *et al.* 2005). Lovekamp-Swan *et al.* suggested that phthalates activate both PPAR α and PPAR γ in cultured rat granulosa cells, resulting in the complete inhibition of aromatase (Lovekamp-Swan *et al.* 2003). However, only a few studies in PPAR α -null mice have suggested that some of the effects of DEHP on fertility are mediated by PPAR α (Peters *et al.* 1997, Ward *et al.* 1998, Gazouli *et al.* 2002). The administration of DEHP resulted in milder testis lesions and higher testosterone levels in PPAR α -null mice than in wild-type mice (Gazouli *et al.* 2002).

The placental effects of PPARs are important for embryonic development (Fig. 3)

PPAR γ is required for the attachment of embryos to the endometrium and the development and function of the placenta (Barak *et al.* 1999). Strong PPAR γ expression has been detected in the trophectoderm and inner-cell mass of the blastocyst (Mohan *et al.* 2002). PPAR γ inactivation leads to impaired placental vascularization, resulting in the death of the embryo. Pregnancy failure can be prevented by replacing PPAR γ -deficient placental cells with wild-type cells (Barak *et al.* 1999, Kubota *et al.* 1999). Similar abnormalities in placental development have been observed in RXR α ^{-/-} mice, suggesting that the PPAR γ -RXR α heterodimer is required for placentation (Wendling *et al.* 1999).

PPAR α , PPAR β/δ and PPAR γ are also expressed in gestational tissues (in the amnion, choriodecidea, and placenta) (Berry *et al.* 2003). PPAR β/δ is strongly expressed during decidualization, and regulates embryo implantation (Lim & Dey 2000, 2002). PPAR β/δ is found around implantation sites, and PPAR β/δ -null mice present placental malformations leading to embryo death during early pregnancy (Barak *et al.* 2002). Prostaglandins are signaling molecules expressed during pregnancy and involved in uterine contraction during parturition. Prostaglandin D₂ (PGD₂), a major prostaglandin produced by the uterus during pregnancy, could be converted *in vivo* into a natural ligand of PPAR γ , 15d-PGJ₂ (Hirata *et al.* 1988), but its biologic role remains to be demonstrated *in vivo*. Of note, 15d-PGJ₂ and PPAR γ are colocalized in trophoblast cells in rat (Asami-Miyagishi *et al.* 2004).

Arachidonic acid derivatives (hydroxyeicosatetraenoic acids), also ligands of PPAR γ (Huang *et al.* 1999), are produced by epithelial cells of the uterus during implantation (Li *et al.* 2004). Inhibition of 12/15-lipoxygenase,

an enzyme involved in the production of these metabolites, dramatically reduces the implantation rate (Li *et al.* 2004). The administration of rosiglitazone overcomes this inhibition and restores the implantation rate (Li *et al.* 2004). Another study has shown that short-term TZD administration (2 days) to pregnant wild-type rats during trophoblast differentiation decreases fetal mortality by 50% (Asami-Miyagishi *et al.* 2004) (Fig. 3a).

A recent study, using a model of endometriosis in rats, showed that 4 weeks of ciglitazone treatment decreased the size of endometrial explants (Lebovic *et al.* 2004). These findings suggest that PPAR γ is involved in the attachment of embryos during pregnancy. In addition, during parturition, the production of prostaglandins by the endometrium, myometrium and fetal membranes increases, inducing contractions of the myometrium during labor. Cyclooxygenase-2 (COX-2) catalyzes prostaglandin production and is downregulated by PPAR γ (Subbaramaiah *et al.* 2001). At the start of parturition, PPAR γ expression decreases and COX-2 production increases slightly in fetal membranes, suggesting that PPAR γ promotes quiescence of the uterus, favoring gestation (Dunn-Albanese *et al.* 2004, Ackerman *et al.* 2005) (Fig. 3b).

Finally, in man, PPAR γ is also expressed in the placenta (cytotrophoblasts and syncytiotrophoblasts). Its activation stimulates the production and secretion of hormones required during pregnancy and fetal development, including human choriongonadotropins and syncytiotrophoblast hormones (human placental growth hormone and leptin) (Tarrade *et al.* 2001). Thus, PPAR γ is essential for the maturation of a functional placenta (Fig. 3).

Conclusion

These recent experiments raise several questions. The first concerns the natural ligands of PPAR γ in different tissues and, more precisely, in reproductive tissues expressing this receptor. PPAR γ may play a key role in linking lipid metabolism and reproduction in general. It would be of interest to investigate the impact of different types of fatty acid, integrated into food, on ovulation capacity and fetal development. Another important question is whether the positive effects obtained with TZDs in PCOS patients are due to a direct effect on the ovaries or a positive effect on glucose homeostasis. Additional experiments are now required to increase our knowledge of the way in which lipid metabolism influences reproductive function.

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