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

P Froment, F Gizard1, D Defever2, B Staels1, J Dupont3 and P Monget3

INSERM U.418, UMR Communications Cellulaire et Différenciation, Hôpital Debrousse, 29 rue Soeur Bouvier, 69322 Lyon, France
1INSERM U.545, Institut Pasteur de Lille et Faculté de Pharmacie Université de Lille 2, 1 rue du Pr Calmette, 59019 Lille, France
2LMCB, Department of Molecular Biomedical Research, V.I.B., Technologiekpark 927, B-9052 Ghent (Zwijnaarde), Belgium
3Physiologie de la reproduction et des comportements, UMR 6175 INRA-CNRS-Université F. Rabelais de Tours-Haras Nationaux, 37380 Nouzilly, France

(Requests for offprints should be addressed to P Froment; froment@lyon.inserm.fr)

Abstract

Peroxisome proliferator-activated receptors (PPARα, PPARβ/δ and PPARγ) 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 PPARγ, 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 PPARγ 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 PPARγ. 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.


Introduction

PPARγ is a nuclear receptor of the peroxisome proliferator-activated receptor family, which also includes PPARα and PPARβ/δ (for review, see Sorensen et al. 1998, Desvergne & Wahli 1999). PPARγ 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 PPARγ in adipose cells. TZDs are frequently administered to patients with insulin resistance associated with type II diabetes (for review, see Houseknecht et al. 2002, Gumell 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, PPARγ 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 hypothalamic-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). PPARγ 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 PPARγ acts also as a fuel sensor in reproductive compartments to inform cells on the energy status. In this case, PPARγ 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 PPARγ 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). PPARγ 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, PPARγ 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, PPARγ may play a role in temperature regulation, as its natural ligand is 15d-PGJ2 (15-deoxy-delta12,14-prostaglandin J2), which is secreted into the cerebrospinal fluid (Mouihate et al. 2004). Despite its presence in these organs, PPARγ 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 (Braisant et al. 1996, Elbrecht et al. 1996, Bhattacharya et al. 2005). PPARα and PPARβ/δ are widely expressed in interstitial Leydig cells and seminiferous tubule cells (Sertoli and germ cells) (Braisant et al. 1996, Schultz et al. 1999). On the other hand, PPARγ is thought to be restricted to Sertoli cells (Elbrecht et al. 1996, Corton & Lapinskas 2005). However, Thomas et al. (2005) recently detected PPARγ 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, PPARα- and PPARβ/δ-null mice are viable and fertile (Lee et al. 1995, Peters et al. 2000). Xenobiotic ligands of PPARγ and PPARα induce the translocation of these receptors to the nucleus of Sertoli cells (Bhattacharya et al. 2005). PPARγ is also more strongly expressed in human testicular cancer cells than in normal testicular tissues. PPARγ 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 PPARα 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. PPARγ 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, PPARα 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 PPARα and PPARβ/δ isoforms are expressed primarily in the theca and stroma tissues. PPARα deletion has no apparent effect on the fertility of mice, but the deletion of PPARγ and PPARβ/δ does have this effect (Lee et al. 1995, Peters et al. 2000, Barak et al. 2002). In the ovaries of rodents and ruminants, PPARγ 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). PPARγ is detected early in folliculogenesis, at the primary/secondary follicle stage (Komar 2005). PPARγ 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).

PPARγ 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
Figure 1 Expression of PPARγ in gonads. (a) PPARγ is strongly expressed in granulosa cells in primary to preovulatory follicles in the ovary (human, rat, mouse and ewe). (b) PPARγ 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, PPARγ is detected primarily in the Sertoli cells, with weak expression in spermatocytes. The names of the cells expressing PPARγ 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-beta-hydroxysteroid-dehydrogenase (3-BHSD) and aromatase) than a direct effect of PPARγ 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-BHSD 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 3β-HSD, whereas it decreased the release of progesterone. These results suggest that TZDs decrease the activity of the 3β-HSD enzyme. Moreover, no effect on the amount of Cyp11a1 and 3-BHSD 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 PPARγ was recently shown to downregulate aromatase gene expression via the NF-kB pathway (Fan et al. 2005).

In addition to the effects of PPARγ 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, PPARγ 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).

**PPARγ action in corpus luteum** In cattle, the expression of PPARγ in corpus luteum increases after ovulation. However, if no fertilization or embryo implantation occurs, the corpus luteum regresses and PPARγ 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 PPARγ levels in the ovaries (Sato et al. 2004). In mice, the tissue-specific deletion of PPARγ 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, PPARγ 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 PPARγ 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-Sharif et al. 1999). PPARγ 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 PPARγ in granulosa cells and PPARγ and PPARα in ovarian macrophage cells. TZD treatment decreased expression of inducible NOS (iNOS) in ovarian macrophage cells (Minge et al. 2006). We can speculate that the diminution of PPARγ 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 PPARγ in steroidogenesis and prostaglandin production. Other studies suggest that PPARγ 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.
and the progesterone secretion by corpus luteum (Fraser et al. 2000). In a human macrophage model and in human vascular smooth muscle cells, PPARγ upregulated VEGF (Bamba et al. 2000, Yamakawa et al. 2000), suggesting that PPARγ 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?

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

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 & Kuttenn 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).

www.endocrinology-journals.org
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, Selı & 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 glucose-neogenesis 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. 2005). Interestingly, we recently showed that AMPK is expressed in rat ovary. Its activation decreased 3β-HSD protein levels and reduced progesterone production in cultured rat granulosa cells (Tosca et al. 2005). As with PPARγ, 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 PPARγ 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 PPARγ 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, PPARγ 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 (Bretenthaler 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 (Bjornstorpg 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, PPARγ 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 PPARγ 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 PPARγ during gestation and parturition. (a) PPARγ plays a key role in placental maturation (placental vascularization and placental hormone secretion). PPARγ favors the maintenance of gestation by decreasing COX-2 production, stimulating progesterone secretion and reducing endometrial inflammation. (b) During labor, PPARγ 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. PPARα and PPARγ 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 PPARα and PPARγ in cultured rat granulosa cells, resulting in the complete inhibition of aromatase (Lovekamp-Swan et al. 2003). However, only a few studies in PPARα-null mice have suggested that some of the effects of DEHP on fertility are mediated by PPARα (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 PPARα-null mice than in wild-type mice (Gazouli et al. 2002).

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

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

PPARα, PPARβ/δ and PPARγ are also expressed in gestational tissues (in the amnion, choriodecidua, and placenta) (Berry et al. 2003). PPARβ/δ is strongly expressed during decidualization, and regulates embryo implantation (Lim & Dey 2000, 2002). PPARβ/δ is found around implantation sites, and PPARβ/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 PPARγ, 15d-PGJ2 (Hirata et al. 1988), but its biologic role remains to be demonstrated in vivo. Of note, 15d-PGJ2 and PPARγ are colocalized in trophoblast cells in rat (Asami-Miyagishi et al. 2004).

Arachidonic acid derivatives (hydroxyicosatetraenoic acids), also ligands of PPARγ (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 cigitazone treatment decreased the size of endometrial explants (Lebovic et al. 2004). These findings suggest that PPARγ 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 PPARγ (Subbaramaiah et al. 2001). At the start of parturition, PPARγ expression decreases and COX-2 production increases slightly in fetal membranes, suggesting that PPARγ promotes quiescence of the uterus, favoring gestation (Dunn-Albanese et al. 2004, Ackerman et al. 2005) (Fig. 3b).

Finally, in man, PPARγ 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 choriogonadotropins and syncytiotrophoblast hormones (human placental growth hormone and leptin) (Tarrade et al. 2001). Thus, PPARγ 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 PPARγ in different tissues and, more precisely, in reproductive tissues expressing this receptor. PPARγ 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.

Acknowledgements

The authors thank A Edelman and J Sappa for expert language revision. The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.
References


Brettenhaller N, De Geyter C, Huber PR & Keller U 2004 Effect of the insulin sensitizer pioglitazone on insulin resistance, hyperandrogenism, and ovolitary dysfunction in women with polycystic ovary syndrome. *Journal of Clinical Endocrinology and Metabolism* 89 3835–3840.


Lovekamp-Swan T, Jetten AM & Davis BJ 2003 Dual activation of PPARalpha and PPARgamma by mono-(2-ethylhexyl) phthalate in rat ovarian granulosa cells. *Molecular and Cellular Endocrinology* 201 133–141.


