REVIEW

The interleukin-1 system and female reproduction

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Abstract

Interleukins (ILs) are known best for their involvement in the immune system and their role during inflammation. In the ovary, a growing body of evidence suggests that the ovarian follicle is a site of inflammatory reactions. Thus ovarian cells could represent sources and targets of ILs. Since then, the IL-1 system components (IL-1α, IL-1β, IL-1 receptor antagonist, IL-1 receptors) have been demonstrated to have several sites of synthesis in the ovary. These factors have been localized in the various ovarian cell types, such as the oocyte, granulosa and theca cells, in several mammalian species. IL-1-like bioactivity has been reported in human and porcine follicular fluid at the time of ovulation. The role of IL-1 in local processes is still poorly known, although there is evidence for involvement in the ovulation process, and in oocyte maturation. More precisely, IL-1 may be involved in several ovulation-associated events such as the synthesis of proteases, regulation of plasminogen activator activity, prostaglandin and nitric oxide production. IL-1 also regulates ovarian steroidogenesis. These different aspects of the involvement of the IL-1 system in important aspects of female reproduction are discussed.

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Introduction

Interleukins (ILs) are polypeptide cytokine components of the immune system that were originally defined by their action between leukocytes. IL-1 was first described in 1972 by Géry and Waksman (Géry & Waksman 1972). Identified as a lymphocyte-activating factor, it was named IL-1 in 1979 at the 2nd International Congress on Lymphokines. IL-1 is organized as a gene system that includes two bioactive ligands, IL-1α and IL-1β, and one natural receptor antagonist (IL-1ra). These three molecules are encoded by separate genes and bind to two types of receptors: type 1 (IL-1R1) and type 2 receptors (IL-1R2). IL-1 is produced by a large variety of cells and acts as a paracrine/autocrine factor on target cells. Mice deficient in components of the IL-1 system are widely studied in order to better understand its implication in various physiological processes (Fantuzzi 2001). In the ovary, several studies led to the hypothesis that in mammalian species, IL-1 is a paracrine factor that could be involved in the cascade of events that lead to ovulation (Ben-Shlomo & Adashi 1994). This review focuses on the impact of the IL-1 system on ovarian function and physiology.

The components of the IL-1 system

IL-1α and IL-1β

Cloning IL-1 showed that two separate genes encode two different types of IL-1. IL-1α and IL-1β have been cloned in humans (March *et al.* 1985), mice (Lomedico *et al.* 1984, Gray *et al.* 1986), rats (Nishida *et al.* 1988), rabbits (Furutani *et al.* 1985, Mori *et al.* 1988) and horses (Howard *et al.* 1998). IL-1α and IL-1β can either be stored in the cell after translation as a precursor (pro-IL-1) of 31 kDa. Pro-IL-1α is as biologically active as the mature form. It acts intracellularly (Roux-Lombard 1998).

Mature forms are synthesized after cleavage of the precursor forms by IL-1-converting enzyme or caspase 1 (cysteine-containing proteinases cleaving behind aspartate). IL-1α and IL-1β display amino acid and nucleotide homologies of 26 and 45% respectively in humans (Dower *et al.* 1986). Kurt-Jones *et al.* (1985) and Bailly *et al.* (1990) have demonstrated the existence of a transmembrane IL-1α form of 23 kDa. This IL-1α form is bioactive and was demonstrated at the surface of monocytes and B lymphocytes. This form is controversial (Minnich-Carruth *et al.* 1989), and it is generally admitted that IL-1α and β

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are secreted molecules. Nevertheless, they do not contain a conventional peptide signal and the mechanism of their secretion is unknown (Rubartelli *et al.* 1990).

IL-1α and β have similar biological effects. They play an essential role in the inflammatory process and the immune response. For example, they stimulate proliferation and activation of B and T lymphocytes, synthesis of acute phase proteins in the liver, and prostaglandin (PG) production (Oppenheim *et al.* 1986, Martin & Resch 1988, Dinarello 1991, Ribardo *et al.* 2001). IL-1 is mainly secreted by monocytes/macrophages after stimulation by various factors such as endotoxins.

Several publications demonstrate that IL-1 is produced by various tissues such as skin (Luger *et al.* 1981), brain (Giulan *et al.* 1988), testis (Khan *et al.* 1987), and lung, liver and placenta (Granholm & Söder 1991). Its presence has also been demonstrated in ovarian follicular fluid (Khan *et al.* 1988).

IL-1ra

IL-1ra was first detected in the urine of patients with fever or leukemia (Seckinger *et al.* 1987). Then, IL-1ra was detected in supernatants of human monocyte cultures (Eisenberg *et al.* 1990, 1991). IL-1ra regulates IL-1 bioactivity. Indeed, after binding to IL-1Rs, IL-1ra prevents IL-1 binding and does not transduce the intracellular signal. At present, it has been demonstrated that IL-1ra is produced by a large variety of cells, such as monocytes, macrophages, neutrophils, hepatocytes and microglia. Several studies have demonstrated that IL-1ra and IL-1β are produced by the same cell types, but this production activates different pathways (Granowitz *et al.* 1991, Vannier *et al.* 1992). It has been demonstrated that the IL-1ra gene shares 18% homology with IL-1α and 26% homology with IL-1β (Carter *et al.* 1990). In humans, the IL-1ra gene is close to IL-1α and IL-1β genes, which are localized on the long arm of chromosome 2. IL-1ra is a secreted glycosylated protein of 22 kDa (Hannum *et al.* 1990) which can bind to IL-1Rs with the same affinity as IL-1 (Arend & Guthridge 2000). The main function of IL-1ra is to regulate the effects of IL-1 by blocking receptors. This has been clearly demonstrated by using transgenic and IL-1ra knock-out mice (Arend & Guthridge 2000). An alternative splicing of the IL-1ra mRNA gives rise to a modification of the exon coding for the secretion sequence, leading to an intracellular isoform named icIL-1ra (Haskill *et al.* 1991, Butcher *et al.* 1994). Three icIL-1ra isoforms have been described. The biological activity of icIL-1ra 1 and 2 is the same as that of the secreted isoform of IL-1ra. In contrast, icIL-1ra 3 inhibits only slightly the IL-1 binding to its receptors (Arend & Guthridge 2000). IcIL-1ra is expressed constitutively in some cell types, and it has been suggested that icIL-1ra could play a regulatory role in IL-1α bioactivity (Haskill *et al.* 1991).

IL-1Rs

IL-1α, IL-1β and IL-1ra bind to membrane receptors localized on target cells (Dower *et al.* 1986). Two kinds of receptors from the immunoglobulin family have been described. These two receptors are from two different genes but display similarities in their transmembrane and extracellular domains (Martin & Falk 1997). IL-1R1 is a 80 kDa glycoprotein. It was described in 1985 by Dower and colleagues (Dower *et al.* 1985). Its complete sequence contains 567 amino acids with a cytoplasmic part of 213 amino acids (Slack *et al.* 1993, Sims *et al.* 1994). It is expressed by various cell types, such as T cells (Dower *et al.* 1990), fibroblasts (Dower *et al.* 1990) and smooth muscle cells (Cavaillon 1991). IL-1R1 mainly binds IL-1α, pro-IL-1α and IL-1ra. It has only a low affinity for IL-1β (Kilian *et al.* 1986). IL-1R2 has a molecular mass of 60–65 kDa (Matsushima *et al.* 1986, MacMahan *et al.* 1991). Its complete sequence contains 398 amino acids, with a small intracytoplasmic part of 29 amino acids (Slack *et al.* 1993). Thus, several authors have confirmed that IL-1R2 is not able to transduce the signal (Sims *et al.* 1993) and would only participate in the bioavailability of ligands such as IL-1β (Colotta *et al.* 1994). This receptor is expressed by B and T cells, monocytes and placenta (Cavaillon 1991), as well as in the mouse brain (Gabellec *et al.* 1996). IL-1R2 displays a higher affinity for IL-1β than for IL-1α (Roux-Lombard 1998). The IL-1 biological activity regulation is complex because soluble forms of receptors have been described (Symons *et al.* 1991). These soluble receptors result from a proteolytic cleavage of the extracellular part of membrane receptors. They inhibit, by binding IL-1 extracellularly, the binding of IL-1 to membrane receptors, and thus act as inhibitory factors since no signal is transmitted within the cell. It has been demonstrated that the soluble form of type 1 receptor preferentially binds to IL-1α and IL-1ra, whereas the soluble form of type 2 receptor binds to IL-1β with a higher affinity (Roux-Lombard 1998).

The IL-1 system in the ovary

The ovarian expression sites of the IL-1 members have been studied in several species (Machelon & Emilie 1997). Some contradictory results have been obtained, suggesting some species-specific features. The potential production sites for the IL-1 system components are summarized in Fig. 1.

IL-1α and IL-1β

In 1988, some IL-1 biological activity was measured for the first time in human follicular fluid (Khan *et al.* 1988). This result has been then confirmed in humans (Barak *et al.* 1992, Wang & Norman 1992, Jasper & Norman 1995)

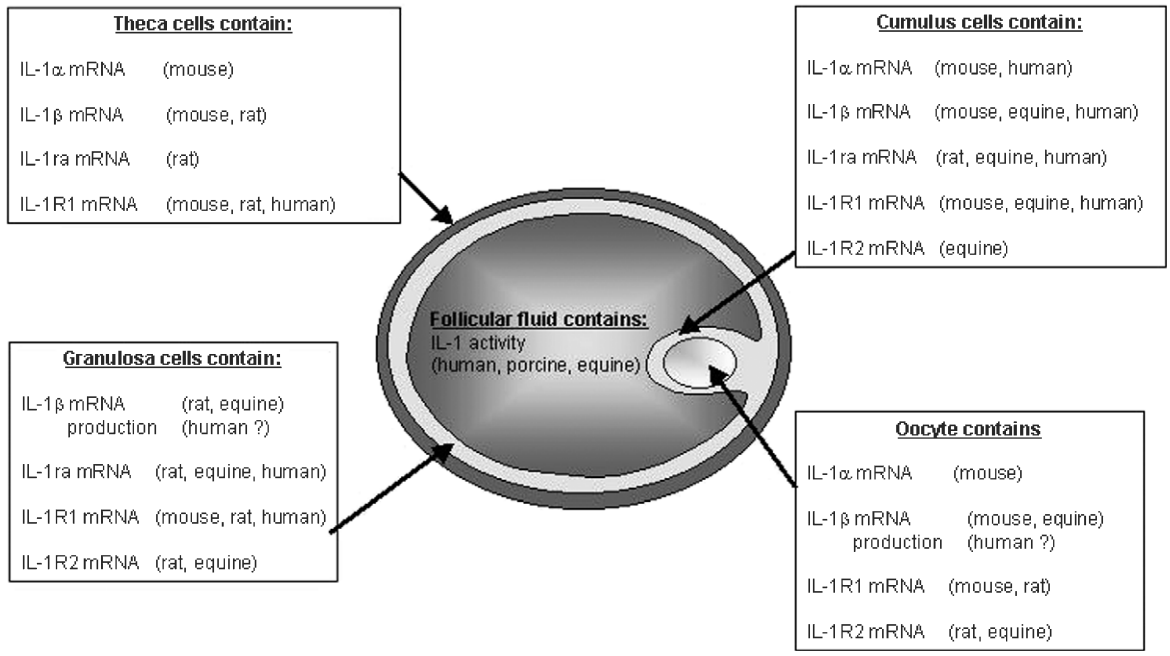

Figure 1 Localization of the IL-1 system components in the ovarian follicle of mammalian species. Related gene expression and/or protein production are shown according to data available in the literature. (?) indicates controversial results.

and pigs (Takakura *et al.* 1989). This biological activity could result in part from some local IL-1 production by ovarian cells (granulosa and/or theca cells). De Los Santos *et al.* (1998) demonstrated in women involved in *in vitro* fertilization trials that cumulus cells express IL-1α and IL-1β mRNA. This observation confirms the study performed by Barak *et al.* (1992). Recently, Carlberg *et al.* (2000) have confirmed that human granulosa cells secrete IL-1β *in vitro*. These results contrast with a previous study showing that human granulosa and theca cells do not contain mRNA coding for IL-1β (Hurwitz *et al.* 1992). These conflicting observations could be explained by the high individual variability among the cells from the women participating in these studies. Some recent work has shown a correlation between intrafollicular levels of IL-1 and the quality of the oocyte in terms of embryos after *in vitro* fertilization (Karagouni *et al.* 1998, Mendoza *et al.* 1999). Finally, IL-1β mRNA and proteins have been localized in human embryos at the time of fertilization, suggesting their presence in the mature oocyte (De Los Santos *et al.* 1996). This study confirms the results obtained by Zolti *et al.* (1991), who showed some IL-1 bioactivity in culture media from human oocytes, cumulus cells and embryos. In the mouse, the ovarian synthesis of IL-1α and IL-1β was first detected by *in situ* hybridization (Takacs *et al.* 1988). Patterns change during follicular development. IL-1α and β are first observed in the theca interna from growing follicles and in the oocyte (Simon *et al.* 1994, Terranova & Montgomery-Rice 1997). At the time of preovulatory maturation, after the luteinizing hormone (LH) surge or human chorionic gonadotropin (hCG) injection, high levels of IL-1α and IL-1β are observed in cumulus cells (Simon *et al.* 1994). In rats, IL-1β mRNA was localized by *in situ* hybridization in theca cells after hCG injection (Hurwitz *et al.* 1991). This result was confirmed by Kol *et al.* (1999*a*). In the same study, these authors showed the presence of IL-1β mRNA in granulosa cells, and demonstrated the existence of an intrafollicular IL-1β surge at the time of ovulation as previously demonstrated by Brännström *et al.* (1994). They also demonstrated that ovarian cells synthesize IL-1α and that this production is IL-1β-dependent (Kol *et al.* 1999*b*). Recently, we demonstrated the presence of IL-1β mRNA in equine cumulus–oocyte complexes (Martoriati *et al.* 2002). The IL-1β mRNA level varies during *in vivo* and *in vitro* maturation (Martoriati *et al.* 2002). Moreover, IL-1β mRNA has been demonstrated in equine granulosa cells, whereas immunoreactive IL-1β has been observed in follicular fluids from preovulatory follicles (Martoriati & Gérard 2003).

IL-1ra

Only few studies have addressed the localization of the IL-1 receptor antagonist in the ovary. In 1992, RNA extraction from human ovarian fragments allowed for the first time the detection of IL-1ra mRNA in this tissue (Hurwitz *et al.* 1992). More precisely, these authors demonstrated that human granulosa cells totally devoid of immune cells synthesize IL-1ra. Then, IL-1ra was

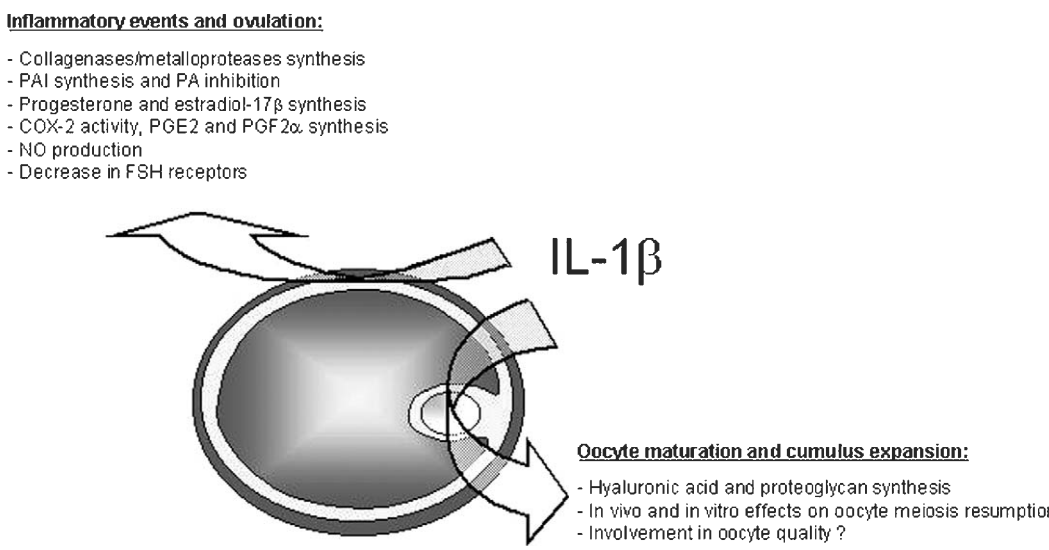

Figure 2 A summary of the potential roles of IL-1β in the mammalian ovarian follicle. PAI, plasminogen activator inhibitors; PA, plasminogen activator; COX-2, cyclooxygenase-2; PG, prostaglandin; NO, nitric oxide; FSH, follicle-stimulating hormone.

localized by *in situ* hybridization in granulosa and cumulus cells from rat antral follicles (Kol *et al.* 1999*c*). With this technique, IL-1ra mRNA has never been detected in primordial follicles, whereas it was abundantly expressed in granulosa and theca cells from growing follicles (Wang *et al.* 1997). IL-1ra has been detected by RT-PCR in human (De Los Santos *et al.* 1998) and equine (Martoriati *et al.* 2002) cumulus cells. IL-1ra mRNA has been also demonstrated in equine granulosa cells, and its quantity varies during preovulatory maturation (Martoriati & Gérard 2003).

IL-1R1 and IL-1R2

IL-1R1 was first detected in human granulosa and theca cells (Hurwitz *et al.* 1992). IL-1R1 mRNA is expressed neither by the human oocyte (De Los Santos *et al.* 1998) nor by the equine oocyte (Martoriati *et al.* 2002), but it is present in cumulus cells of both species (De Los Santos *et al.* 1998, Martoriati *et al.* 2002), and in human embryos (De Los Santos *et al.* 1998). The expression sites of IL-1R1 vary with follicular development in the mouse. IL-1R1 mRNA is synthesized by theca cells from growing follicles. Before ovulation, IL-1R1 mRNA is expressed by cumulus and granulosa cells. It is abundantly expressed in the mouse oocyte all along follicular development (Simon *et al.* 1994), contrary to the human oocyte. In the rat, data concerning IL-1R1 ovarian localization are contradictory. IL-1R1 mRNA has been localized by *in situ* hybridization in the granulosa and theca cells of immature ovaries, and in the oocyte at the time of ovulation (Kol *et al.* 1999*a*). Scherzer *et al.* (1996) have also shown the presence of IL-1R1 in granulosa cells from immature rats, whereas Wang *et al.* (1997) have demonstrated that IL-1R1 mRNA is present in granulosa and theca cells from growing follicles but absent from primordial and preantral follicles. Moreover, in rat preovulatory follicles, IL-1R1 mRNA is more abundant in theca cells than in granulosa cells (Wang *et al.* 1997), leading to the hypothesis that in the rat IL-1 acts on granulosa cells during follicular development and on theca cells at the time of ovulation.

IL-1R2 has not been much studied. IL-1R2 mRNA has not been detected in the ovary of immature rats (Kol *et al.* 1999*a*), but has been demonstrated in cultured ovarian cells. We showed recently by RT-PCR that IL-1R2 mRNA is synthesized in equine cumulus cells and oocytes, before and after *in vitro* maturation (Martoriati *et al.* 2002). Moreover, in contrast to IL-1R1, IL-1R2 mRNA is expressed in equine granulosa cells, but its level does not vary significantly during final follicular maturation (Martoriati & Gérard 2003).

Roles of the IL-1 system in the ovary

During the inflammatory process, numerous mechanisms are activated against infection, such as synthesis of proteolytic enzymes and production of PGs and nitric oxide (NO). Pro-inflammatory cytokines in general, and IL-1 in particular, are initiatory and regulatory factors of these mechanisms. Some of them are observed in the ovary during the periovulatory period. IL-1 has thus been hypothesized to be involved in the ovulatory process, as well as in some ovarian function such as steroidogenesis. The functions discussed below are summarized in Fig. 2.

Roles of IL-1 in ovulation and in oocyte maturation

Several studies have demonstrated directly or indirectly that IL-1 may intervene in oocyte maturation and ovulation. In *ex vivo* perfused ovaries used as model, IL-1β induces ovulation (in the rat: Brännström *et al.* 1993*a*, Van der Hoek *et al.* 1998; in the rabbit: Takehara *et al.* 1994) similarly to LH or hCG. In the rat, IL-1β potentiates the inductive ovulatory effect of LH by increasing the rate of ovulated oocytes (Brännström *et al.* 1993*a*). In the mare, the intrafollicular injection of IL-1β at the preovulatory stage mimics the effect of an i.v. injection of gonadotropins by inducing ovulation (Martoriati *et al.* 2003). In contrast, the use of IL-1ra in the perfusion medium (Peterson *et al.* 1993), by intraovarian injection (Simon *et al.* 1994), or by intrafollicular injection (Martoriati *et al.* 2003) reduces the ovulation rate or delays the ovulation time. These studies have confirmed that IL-1 is involved in ovulation, and that this effect is mediated by a specific receptor.

There are not many results on the oocyte–cumulus complex and they are contradictory. In the rat, the ovarian perfusion model allowed the demonstration that IL-1β has no effect on meiosis resumption of oocytes (Brännström *et al.* 1993*a*). In the rat, the intraovarian injection of IL-1ra decreases the expansion rate of cumulus cells (Simon *et al.* 1994), which may explain the decreased ovulation rate observed. In the rabbit, IL-1β ovarian perfusion induces oocyte meiosis resumption and ovulation (Takehara *et al.* 1994). Recently in the mare, we demonstrated that the intrafollicular injection of IL-1β increases the oocyte maturation rate (Martoriati *et al.* 2003). The effect of IL-1β on oocytes could be mediated via cumulus cells.

Taken together, these results highlight that the effects of IL-1β on oocyte maturation are contradictory and may be species-dependent.

Role of IL-1 in inflammatory-linked mechanisms in the ovary

Production and activation of proteolytic enzymes Hurwitz *et al.* (1993) have demonstrated that *in vitro* treatment of rat ovarian cells with IL-1β leads to the accumulation in the culture medium of a 92 kDa gelatinase. Its expression is IL-1β dose-dependent and inhibited by IL-1ra. This gelatinase could be involved in the ovulatory process. In contrast, IL-1β inhibits plasminogen activator activity in cultured preovulatory follicles (Bonello *et al.* 1995). IL-1β acts predominantly by activating some plasminogen activator inhibitors (Hurwitz *et al.* 1994, Piquette *et al.* 1994, Karakji & Tsang 1995).

PG production PGs are important factors involved in the ovulatory process, since injection of inhibitors blocks ovulation (Wallach *et al.* 1975, Ainsworth *et al.* 1979, Watson & Sertich 1991, Brännström 1993). The ovarian production of PGs and its regulation has been studied by several authors. Their results lead us to conclude that IL-1 intervenes in PG production, mainly by acting on cyclooxygenase-2 (COX-2) synthesis. Actually, IL-1β induces *in vitro* PGE2 and PGF2α production by granulosa cells (humans: Watanabe *et al.* 1993; rats: Hurwitz *et al.* 1995; cattle: Acosta *et al.* 1998). Moreover, it has been demonstrated *in vitro* that IL-1β induces an increase in 6 keto-PGF1α, PGE2 and PGF2α in cultured rat preovulatory follicles (Brännström *et al.* 1993*b*) and bovine granulosa cells (Nothnick & Pate 1990). This effect may be triggered by sphingomyelin hydrolysis and ceramide production (Santana *et al.* 1996). Finally, *in vivo* IL-1β concentration in human follicular fluid is correlated with PGE2 and PGF2α concentrations (Watanabe *et al.* 1994). By using an ovarian perfusion model, Peterson *et al.* (1993) confirmed these observations in the rat. More precisely, the mechanisms by which IL-1β regulates PG production and action have been studied. Narko *et al.* (1997) demonstrated that IL-1β induces *in vitro* COX-2 mRNA synthesis in human granulosa–luteal cells. This has been confirmed in rat granulosa cells (Ando *et al.* 1999) and mouse cumulus cells (Joyce *et al.* 2001). Narko *et al.* (2001) have shown that IL-1β induces PGF2α receptor mRNA synthesis as well as EP2 and EP4 (two PGE2 receptor sub-types) mRNA synthesis in human granulosa cells.

IL-1 also induces an increase in A2 phospholipase activity (Townson & Pate 1994, Kol *et al.* 1997), induces the synthesis of PGS2 (Narko *et al.* 1997, Ando *et al.* 1998) and stabilizes its mRNA (Saito *et al.* 2001). This effect may be triggered by ceramides (Irahara *et al.* 1999). Interestingly, Davis *et al.* (1999) demonstrated that IL-1β is able to restore ovulation in mice carrying a null mutation for COX-2, and which thus fail to ovulate.

NO production Ahsan *et al.* (1997) have shown that IL-1 can induce NO production in the ovary. In humans, Tao *et al.* (1997) have demonstrated that follicular cells incubated 24 h in the presence of IL-1β show an increased ability to produce NO. IL-1β is able to inhibit apoptosis in rat ovarian follicles, by increasing NO production (Chun *et al.* 1995). Addition of IL-1ra blocks these effects, leading to the hypothesis that IL-1β acts via a specific receptor. A study performed by Ben-Shlomo *et al.* (1994) showed that cell communications between granulosa and theca cells play a central role in NO ovarian production.

Cellular metabolism During terminal follicular maturation, the energy metabolism is profoundly changed (Billig *et al.* 1983). IL-1β increases lactate accumulation in cultured rat ovarian cells, and glucose consumption and transport in a time-, dose- and receptor-dependent manner. Granulosa–theca interactions are essential (Ben-Shlomo *et al.* 1997).

Steroidogenesis Numerous studies have focused on the effect of IL-1 on steroidogenesis. *In vitro* studies have demonstrated that IL-1β inhibits granulosa cell

progesterone production in various species (rat: Gottschall *et al.* 1987, 1988, Kasson & Gorospe 1989, Brännström *et al.* 1993*b*; pig: Fukuoka *et al.* 1989; rabbit: Bréard *et al.* 1998). On the contrary, progesterone production by granulosa cells is increased *in vitro* by IL-1β in cattle (Baratta *et al.* 1996), and by IL-1α in humans (Sjogren *et al.* 1991), as well as in hamster preovulatory follicles (Nakamura *et al.* 1990). This effect may be triggered by sphingomyelin hydrolysis and ceramide production (Santana *et al.* 1996). Other studies have demonstrated no obvious effect of IL-1β on progesterone production (cattle: Nothnick & Pate 1990, Acosta *et al.* 1998; woman: Barak *et al.* 1992). Furthermore, IL-1 may have some effect on estradiol-17β production. It has been shown *in vitro* in human granulosa cells that IL-1β inhibits estradiol-17β production (Barak *et al.* 1992), most probably by increasing NO production (Tobai & Nishiya 2001). IL-1 could also inhibit P450 aromatase activity (Yasuda *et al.* 1990, Ghersevich *et al.* 2001) as well as other enzymes involved in estradiol-17β synthesis (Hurwitz *et al.* 1991, Ghersevich *et al.* 2001). A similar result was observed in cattle (Baratta *et al.* 1996). In rat granulosa cells, Gottshall *et al.* (1989) and Zhou & Galway (1991) have demonstrated a dose-dependent inhibition of IL-1β on the follicle-stimulating hormone (FSH) estrogen production. The effect of IL-1β on FSH receptor can be hypothesized, since in the rat ovary IL-1β decreases the quantity of gonadotropin receptors (Gottshall *et al.* 1987, 1988, Kasson & Gorospe 1989).

Conclusions

The data reviewed above provide substantial evidence for the existence of a local ovarian IL-1 system. Despite the apparent preliminary nature of the observations, there is every reason to believe that IL-1 play a major role throughout the ovarian life cycle, in particular in the ovulatory process. Future investigations will most likely reveal important data relevant to the pathways of IL-1 production, regulation and actions. These will help toward a fuller understanding of IL-1 involvement in the ovarian function and female fertility.

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