

# Role of prolactin in the regulation of ovarian function in pigs

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## Introduction

Prolactin has proliferative and differentiative effects on numerous types of cells derived from several animal species (Nicoll, 1974). Among these various functions of prolactin is a role in the regulation of reproductive processes in mammals. In this paper we present the results of investigations concerning the influence of prolactin on the pig ovary, both *in vitro* and *in vivo*. Moreover, to present the progress of studies on mechanisms of prolactin action on ovarian cells, we include the results of studies performed on rats, in which the role of prolactin in the regulation of ovarian functions is well known.

## Changes in blood concentrations of prolactin during the oestrous cycle of sows

During the oestrous cycle in pigs there are two periods during which prolactin secretion has been shown to be elevated. One occurs 4-5 days before oestrus and the other during the phase of sexual receptivity. Although this phenomenon is observed with a great regularity in sows (Dusza & Krzymowska, 1979; Brinkley, 1981; Van de Wiel *et al.*, 1981; Prunier *et al.*, 1987), it does not always occur in gilts (Van Landeghem & Van de Wiel, 1977; Pinkert *et al.*, 1988). Our studies (Dusza *et al.*, 1988) revealed a tendency for synchronization of prolactin and prostaglandin F-2 $\alpha$  pulses in the periluteolytic phase of the oestrous cycle and correlations between prolactin and PGF-2 $\alpha$  concentrations were significant ( $P < 0.01$ ) during the period after luteolysis. On most occasions, PGF-2 $\alpha$  concentration increased and appeared to precede the elevation in prolactin level. These results suggest the existence of a relationship between these hormones during the early follicular stage of the cycle.

During the period of oestrus, every exposure to the boar induced a prolactin peak, the amplitude of which decreased towards the end of oestrus (Prunier *et al.*, 1987; J. Mah, J. E. Tilton & L. Dusza, unpublished). Earlier, Van de Wiel *et al.* (1981) suggested a temporal relationship between high concentrations of prolactin and signs of behavioral oestrus. Data obtained from humans and rodents also indicate the possible existence of such a dependence (Drago, 1984). Although a physiological role for prolactin during the early follicular phase and oestrus in sows appears likely, further investigations are needed to permit interpretation of the relationship between prolactin and PGF-2 $\alpha$  and the role of prolactin in the expression of oestrous behaviour of pigs.

## Prolactin receptors in the pig ovary

The ovary is one of the target tissues for prolactin. Cyclic changes in the specific binding of  $^{125}\text{I}$ -labelled prolactin to pig granulosa cells and corpora lutea have been demonstrated (Rolland

*et al.*, 1976; Jammes *et al.*, 1985; Bramley & Menzies, 1987). Binding of  $^{125}\text{I}$ -labelled prolactin was minimal around the time of ovulation when luteinization of the granulosa cells began. As the corpus luteum developed, binding sites became more numerous (Rolland *et al.*, 1976; Bramley & Menzies, 1987). If pregnancy occurs there is a substantial increase in the observed binding capacity with gestational age (Rolland *et al.*, 1976; Jammes *et al.*, 1985; Bramley & Menzies, 1987). After parturition the number of prolactin receptors in pig corpora lutea decreased rapidly (Jammes *et al.*, 1985).

### Effects of prolactin on steroidogenesis in the corpus luteum during the oestrous cycle

The function of the corpus luteum in various species is subjected to concerted regulation by the gonadotrophins, prolactin, oestrogens and placental factors. Among these hormones prolactin plays a partly unexplained role in the formation and maintenance of a functional corpus luteum. Rats have been most extensively studied with regard to the role of prolactin in the regulation of corpus luteum function. In this species, prolactin surges during pro-oestrus are necessary to stimulate formation of cyclic corpora lutea and their transformation to corpora lutea of pseudo-pregnancy or pregnancy (for review see Smith, 1980). The stimulatory effect of prolactin is a result of an inhibition of the activity of the enzymes responsible for progesterone catabolism, such as  $20\alpha$ -hydroxysteroid dehydrogenase which catalyses reduction of progesterone to its inactive form,  $20\alpha$ -dihydroprogesterone (Lamprecht *et al.*, 1969). Prolactin has also been shown to be indispensable for induction and maintenance of LH receptors (Holt *et al.*, 1976).

Recent investigations from several laboratories have demonstrated that the plasma-borne lipoproteins, high-density lipoprotein (HDL) and low-density lipoproteins (LDL), are precursors for luteal steroidogenesis (for review see Murphy & Rajkumar, 1985) and rat ovaries utilize HDL in preference to LDL. Prolactin enhances lipoprotein concentrations, thereby stimulating progesterone synthesis by the luteal cells of the rat. This finding suggests that prolactin is important for maintenance of membrane receptors for HDL (Murphy & Rajkumar, 1985). Sanchez-Criado *et al.* (1988) have reported that in rats, prolactin acts not only as a luteotrophic factor but may also exert an antiluteolytic action. In addition to its luteotrophic role, prolactin is responsible for the final structural demise of the rat corpus luteum (for review see McNeilly *et al.*, 1982).

A luteotrophic role of prolactin during the oestrous cycle in domestic animals is controversial (for review see McNeilly, 1984). The effect of prolactin on steroidogenesis during the lifespan of the pig corpus luteum has been extensively studied during the past decade. In-vitro studies by Stoklosowa & Gregoraszcuk (1984a, b) and Gregoraszcuk (1983) revealed that prolactin stimulates progesterone secretion in luteal cells during the very early stages of pig luteal function. The influence of prolactin on pig luteal cells was maintained as long as large numbers of theca cells were present in the corpus luteum (Stoklosowa & Gregoraszcuk, 1984b). Studies of the response of small and large pig luteal cells from the early luteal phase (Days 1–3) to prolactin have demonstrated that the amount of progesterone released into the medium by large luteal cells was 5 times higher than that released by the small ones (E. Gregoraszcuk, unpublished). Likewise, Buhr (1987) observed that production of progesterone by large cells isolated from pig corpora lutea on Day 10, 15 or 18 of the oestrous cycle always exceeded that of the small cells. In the presence of prolactin (E. Gregoraszcuk, unpublished) large luteal cells synthesized significantly more progesterone than did control incubations (Table 1), whereas progesterone synthesis by small luteal cells was not altered after addition of prolactin to the medium. However, small as well as large luteal cells had diminished oestradiol- $17\beta$  synthesis after prolactin addition to the medium (Table 1). Similarly, progesterone increased and oestradiol- $17\beta$  synthesis declined in cultured human luteal cells from the early and mid-luteal phases of the menstrual cycle in the presence of low prolactin doses (Alila *et al.*, 1987).

As development of the corpus luteum proceeds, its sensitivity to prolactin changes. In-vitro studies (Cook *et al.*, 1967; Gregoraszcuk, 1983; Przala *et al.*, 1984a) indicated that luteal cells from

**Table 1.** Progesterone and oestradiol-17 $\beta$  secretion by large and small luteal cells of pigs after incubation *in vitro* for 1 or 2 h with prolactin (100 ng/ml)

		Progesterone (ng/10 <sup>5</sup> cells)		Oestradiol-17 $\beta$ (pg/10 <sup>5</sup> cells)	
		Control	Prolactin	Control	Prolactin
Large cells	1st hour	19.3 $\pm$ 0.5	23.3 $\pm$ 1.1	274.7 $\pm$ 1.5	6.3 $\pm$ 1.1**
	2nd hour	28.8 $\pm$ 1.2	44.5 $\pm$ 2.1**	41.3 $\pm$ 2.0	11.4 $\pm$ 0.9**
Small cells	1st hour	4.7 $\pm$ 0.3	4.5 $\pm$ 0.5	6.4 $\pm$ 1.5	2.5 $\pm$ 0.2**
	2nd hour	5.5 $\pm$ 1.0	5.0 $\pm$ 0.8	9.0 $\pm$ 0.9	3.4 $\pm$ 0.6*

\* $P < 0.05$ ; \*\* $P < 0.01$ .

the mid-luteal phase did not exhibit enhanced progesterone secretion when prolactin was added to the medium. Przala *et al.* (1984a) observed that prolactin reduced progesterone production by pig luteal cells from Day 13 of the cycle. High doses of prolactin in the culture medium (1, 5 or 10  $\mu$ g/ml) also inhibited 5 $\alpha$ -dihydrotestosterone, testosterone and oestradiol-17 $\beta$  secretion by luteal cells isolated from pig corpora lutea on the 13th day of the oestrous cycle (Przala *et al.*, 1984b).

Dusza *et al.* (1986) reported an experiment in which injections of highly purified pig prolactin (0.5 mg) via the jugular vein of gilts every 2 h for 36 h on Days 12 and 13 of the cycle caused a pulsatile increase of prolactin concentrations to approximately 100 ng/ml, but did not change progesterone and oestradiol-17 $\beta$  secretion (Fig. 1). Luteotrophic or luteolytic effects after artificial elevation of prolactin concentrations were not observed. However, bromocriptine treatment on Days 14 and 16 of the oestrous cycle caused progesterone concentrations to decrease slowly (Dusza *et al.*, 1983). The results of that study and others (Dusza *et al.*, 1988) suggested a relationship between the secretion of prolactin and PGF-2 $\alpha$  involving the participation of prolactin in the final structural demise of the pig corpus luteum.

The likelihood of a paracrine function of prolactin in the pig ovary was also observed by Einspanier *et al.* (1986), who reported detectable concentrations of mRNA for prolactin in ovarian cells and hence the potential of these cells for the production of prolactin by pig ovaries. The concentration of mRNA for prolactin in luteal cells was higher than in granulosa cells.

The possibility also exists that the corpus luteum of the pig is able to produce progesterone autonomously during the oestrous cycle. The minimal response to LH of small and large luteal cells incubated in media supplied with lipoproteins (HDL and LDL) supports the theory on autonomy of pig corpora lutea (Buhr, 1987).

Collectively, it seems likely that prolactin may act as a luteotrophin in the first days of the oestrous cycle. The role of prolactin in the later periods of the luteal lifespan is at the moment controversial and requires further study.

### Prolactin and steroidogenesis in ovarian follicles

Interest in the direct effect of prolactin on steroidogenesis of the follicular cells has recently expanded and many responses have been reported. Most of those studies were carried out with *in-vitro* systems. The effects of prolactin on the follicular cells were dependent on the dose of prolactin, the presence of other hormones in the culture medium and the stage of differentiation of the granulosa cells.

#### The effect of prolactin on progesterone production by granulosa cells

There are many results indicating that prolactin stimulates progesterone secretion by luteinized rat granulosa cells. A stimulatory effect of prolactin was observed in the presence of FSH and

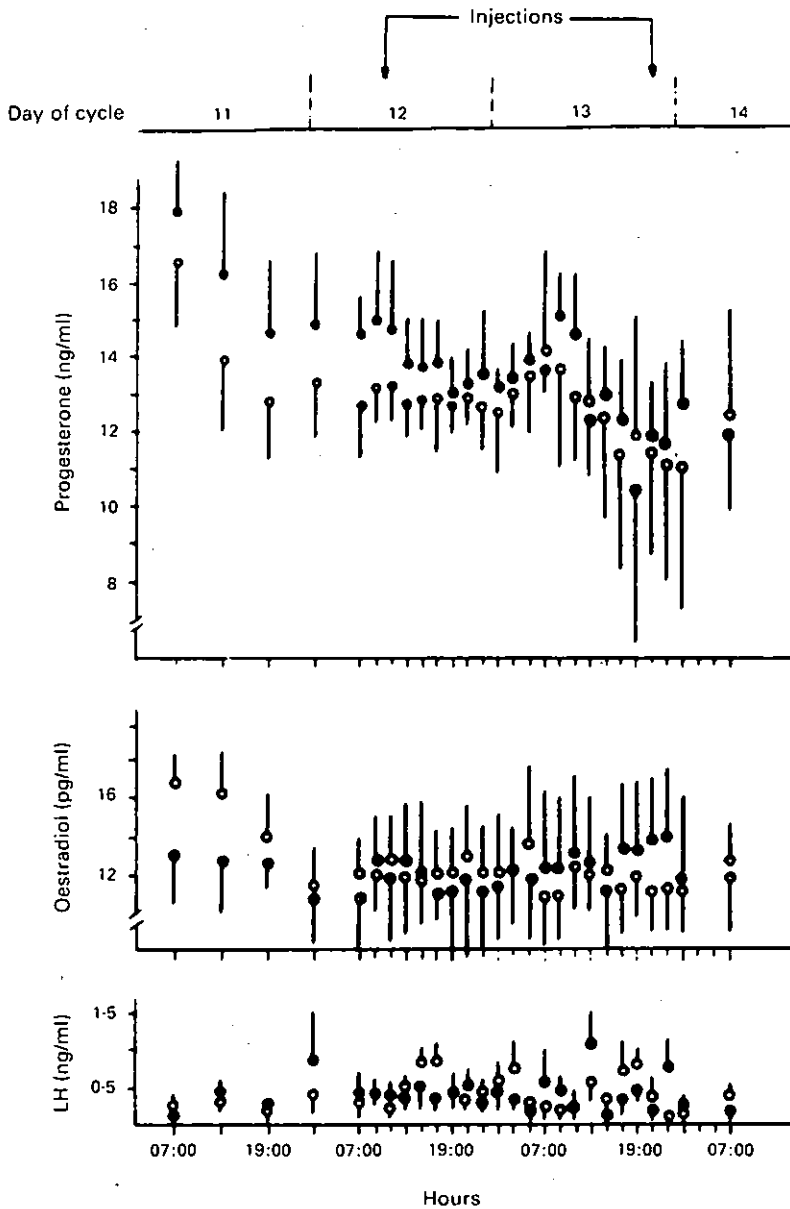


Fig. 1. Mean plasma concentrations of progesterone, oestradiol-17 $\beta$  and LH in gilts after injections of saline (O, N = 6) or prolactin ( $\bullet$ , 0.5 mg/2 h, N = 6) every 2 h for 36 h during the luteal phase.

androstenedione (Wang & Chan, 1982), after preincubation of granulosa cells with FSH, LH and hCG (Alexander & Crisp, 1985; Grasso & Crisp, 1985) and in the presence of FSH and testosterone (Fortune & Vincent, 1986).

The main steroid hormone secreted by pig granulosa cells in culture is progesterone (for review see Stoklosowa, 1988). Pig granulosa cells isolated from medium-size (4–6 mm) follicles (Rajkumar *et al.*, 1988) and large mature > 6 mm follicles (Veldhuis *et al.*, 1980) responded to the addition of prolactin with an increase of progesterone secretion. Provision of lipoprotein substrates (either

LDL or HDL) enhanced progesterone accumulation by pig granulosa cells in culture (Rajkumar *et al.*, 1988). An increase in progesterone secretion was also observed after addition of prolactin or LH in combination with oestradiol-17 $\beta$  in the presence of HDL or LDL and it suggested that prolactin, LH and oestradiol interact in the utilization of extracellular lipoprotein substrate for progesterone synthesis. Stoklosowa & Gregoraszczyk (1984a; unpublished data) reported that prolactin stimulated progesterone secretion by cultured theca cells. Similar effects were observed in co-cultures of granulosa and theca cells (Stoklosowa, 1988). These results suggest that the theca component stimulated the co-culture system to be more sensitive to prolactin.

An inhibitory effect of prolactin was noted in studies on granulosa cells isolated from small (1–2 mm) immature follicles of pigs (Veldhuis *et al.*, 1980). Therefore, the effect of prolactin on progesterone secretion by pig granulosa cells depends on the degree of their maturity. Oestrogen appears to regulate these divergent actions of prolactin. Veldhuis & Hammond (1980) demonstrated that the action of oestrogen may be bipotential. Acute oestrogen administration produced inhibitory effects whereas prolongation of oestrogen treatment beyond 48 h in culture markedly increased progesterone secretion in the presence of prolactin.

However, *in-vivo* studies (Dusza *et al.*, 1986; L. Dusza, R. Ciereszko, G. Kotwica & S. Okrasa, unpublished) involving prolactin administration to intact gilts (Fig. 2) and sows (Figs 3, 4) during the follicular phase of the cycle showed that the increase in plasma prolactin concentration (to about 100 ng/ml in gilts and to about 45 ng/ml in sows) had no effect on peripheral progesterone concentrations. In sows, progesterone was also determined in the utero-ovarian vein plasma and found to be unaffected by prolactin. During the entire follicular phase the progesterone concentration was low. This suggests that prolactin does not play a role in progesterone synthesis by follicles *in vivo* or that some undefined factor(s) suppresses the effect of prolactin on progesterone secretion *in vitro*.

### The effect of prolactin on follicular secretion of oestrogens and androgens

Numerous studies, both *in vivo* and *in vitro*, provide support for a direct inhibitory effect of prolactin on follicular secretion of oestradiol-17 $\beta$ . Studies in the rat (for review see Dusza, 1988) clearly showed that prolactin inhibits oestradiol-17 $\beta$  secretion by granulosa cells under all experimental conditions.

It has also been observed that high concentrations of prolactin suppressed ovarian oestradiol-17 $\beta$  and oestrone secretion in pigs. Dusza *et al.* (1986) reported that prolactin administration for 60 h during the follicular phase of the oestrous cycle in intact gilts (Fig. 2) decreased the concentrations of oestradiol-17 $\beta$  in peripheral plasma on the 2nd and 3rd day of prolactin treatment. In a later experiment (L. Dusza, R. Ciereszko, G. Kotwica & S. Okrasa, unpublished), designed to describe more precisely the production of ovarian oestrogens and androgens, utero-ovarian venous blood was collected every hour during the follicular phase of the oestrous cycle in sows. Administration of prolactin (0.25 mg pig prolactin *i.v.* hourly for 48 h) evoked divergent changes in ovarian steroid concentrations depending on the time of prolactin administration. When injections of prolactin were initiated in the early follicular phase (Day 15–16), immediately after the decline in progesterone concentration in utero-ovarian vein plasma, an effect of treatment on oestrone concentration was noted, but concentrations of oestradiol-17 $\beta$ , testosterone, 5 $\alpha$ -dihydrotestosterone and androstenedione were not affected (Fig. 3). When prolactin was administered on Day 17–18 of the cycle, secretion of oestrogens and androstenedione was significantly inhibited. The effect on testosterone and 5 $\alpha$ -dihydrotestosterone was less pronounced (Fig. 4). These results indicate that prolactin acts directly on follicular steroidogenesis in the pig. McNeilly & Baird (1983) reported that enhanced plasma concentrations of prolactin induced by repeated (every 2 h) *i.v.* injections of thyrotrophin-releasing hormone during the preovulatory period in the ewe suppressed oestradiol-17 $\beta$  secretion by directly affecting the ovary. The effect of prolactin on the suppression of oestrogens appears to be exerted via inhibition of the induction and/or maintenance of the aromatase

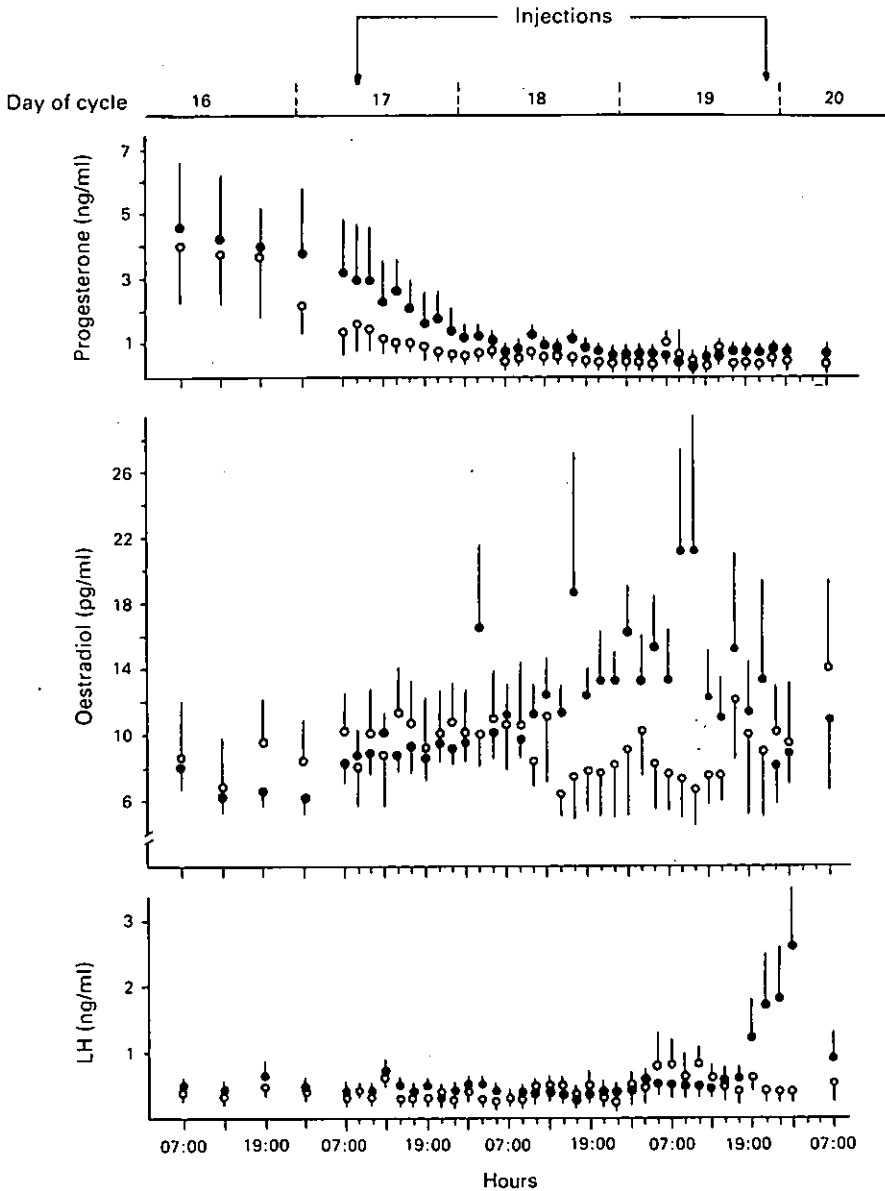


Fig. 2. Mean plasma concentrations of progesterone, oestradiol-17 $\beta$  and LH in gilts after injections of saline (O, N = 6) or prolactin (●, 0.5 mg/2 h, N = 6) every 2 h for 60 h during the follicular phase.

system by FSH. This phenomenon was also observed by Dorrington & Gore-Langton (1981) and Tsai-Morris *et al.* (1983).

Other modes of prolactin action have been suggested by McNeilly *et al.* (1982) and McNeilly (1984): they reported that prolactin inhibited LH-induced androgen production by the theca layer. Magoffin & Erickson (1982) also demonstrated that high concentrations of prolactin could block LH-induced androgen production in rat ovarian interstitial cells. Our results would support the theory that high concentrations of prolactin during the follicular phase of the oestrous cycle in sows

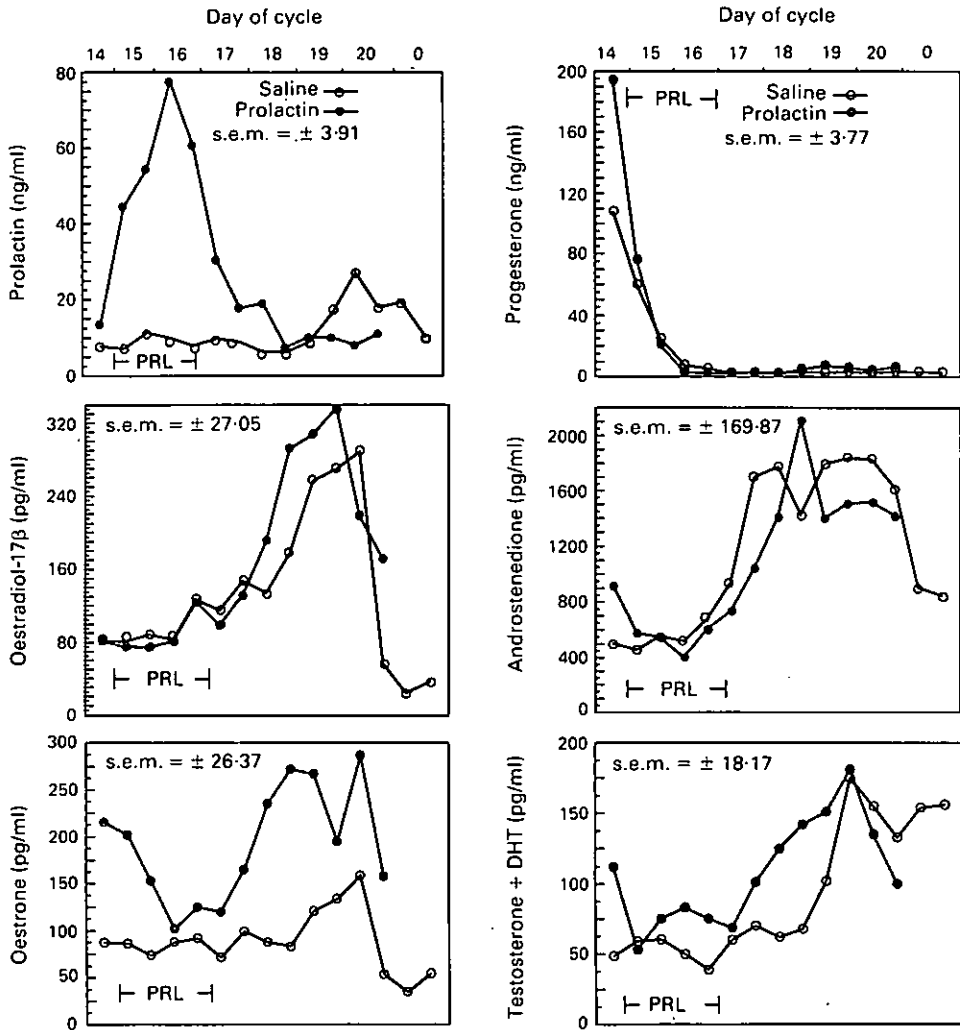


Fig. 3. Jugular vein prolactin and utero-ovarian vein concentrations of progesterone, oestradiol-17 $\beta$ , androstenedione, oestrone and testosterone plus 5 $\alpha$ -dihydrotestosterone in sows after injections of saline (N = 4) or prolactin (0.25 mg/h, N = 2) every 48 h from Day 15 or 16 of the oestrous cycle. Each point represents a mean for 12 h.

might interfere with the production of androgens. We suggest that hyperprolactinaemia produced under certain experimental conditions may be a situation which occurs naturally in lactating sows.

Little is known about the role of prolactin in the growth and development of ovarian follicles. Wang *et al.* (1980) suggested that marked inhibitory action on oestrogen secretion by the granulosa cells could result in the termination of follicular growth and the initiation of atresia in some follicles.

### Role of prolactin in pregnancy and parturition

The role of prolactin in the maintenance of pregnancy in the pig has not been completely delineated. Pregnancy maintenance in the pig is dependent on progesterone produced by the

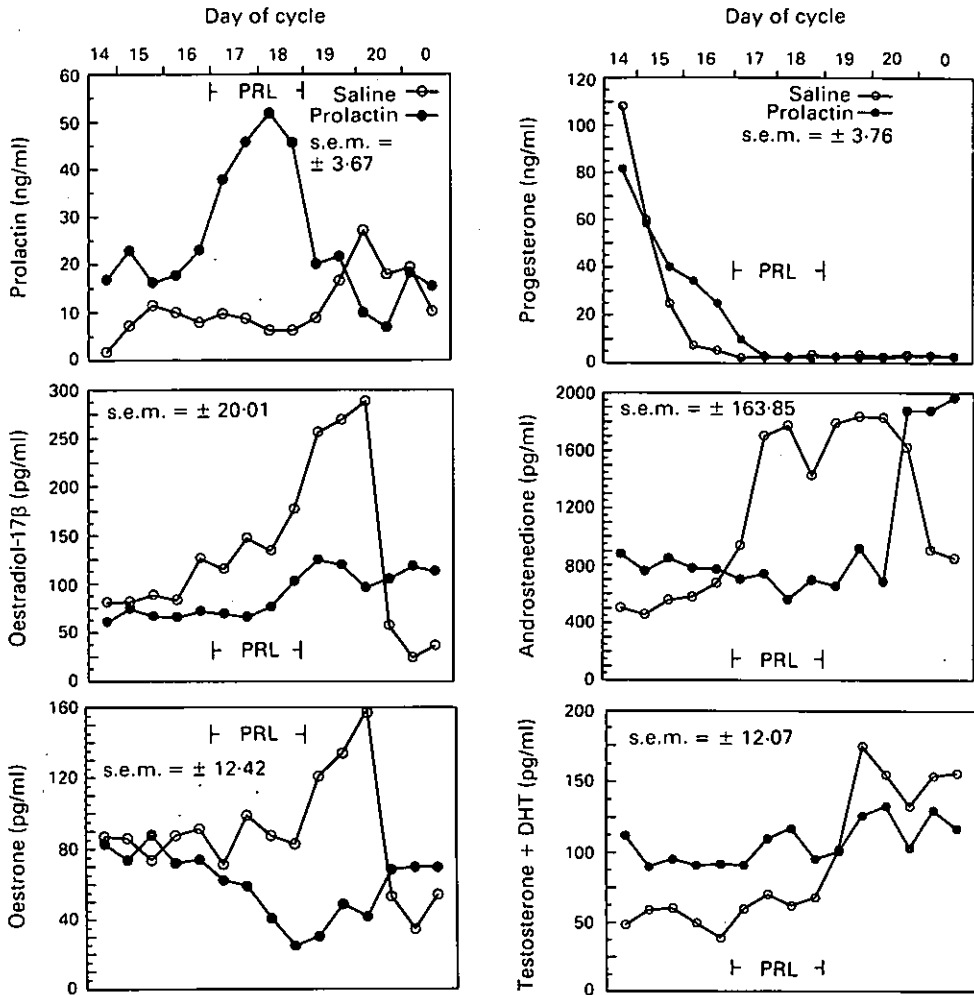


Fig. 4. Jugular vein prolactin and utero-ovarian vein concentrations of progesterone, oestradiol-17 $\beta$ , androstenedione, oestrone and testosterone plus 5 $\alpha$ -dihydrotestosterone in sows after injections of saline (N = 4) or prolactin (0.25 mg/h, N = 4) every 48 h from Day 17 or 18 of the oestrous cycle. Each point represents a mean for 12 h.

corpora lutea (for review see Bazer & First, 1983). Concentrations of prolactin in pregnancy do not differ from the basal concentrations during the oestrous cycle (Dusza & Krzymowska, 1981). However, the number of prolactin receptors has been shown to increase during pregnancy (Rolland *et al.*, 1976; Jammes *et al.*, 1985; Bramley & Menzies, 1987). The rise of prolactin receptors during pregnancy precedes that of LH in the pig corpus luteum and Jammes *et al.* (1985) suggested that prolactin may induce receptors for LH.

Bazer & First (1983), in a review pertaining to pregnancy and parturition in domestic animals, suggested that pig corpora lutea produced progesterone autonomously until Day 14 of pregnancy, while from Day 14 until Day 50 of pregnancy LH acts as a luteotrophic factor. In the second half of pregnancy prolactin was considered to be indispensable for normal luteal function. This hypothesis has been confirmed with in-vitro studies. Cook *et al.* (1967) found no influence of prolactin on progesterone synthesis by slices of pig luteal tissue obtained during the first half of pregnancy. Luteal (Wiesak, 1985), as well as granulosa (Przala *et al.*, 1985), cells isolated from pig ovaries on



Days 18 or 19 of pregnancy did not significantly change their secretion of steroid hormones under the influence of prolactin.

Luteal cells isolated between Days 70 and 95 from corpora lutea of pregnant pigs of pregnancy only significantly increased progesterone secretion when exogenous cholesterol in the form of a lipoprotein complex (LDL or HDL) was provided (Murphy & Rajkumar, 1985; Rajkumar *et al.*, 1985, 1987). These authors suggested that prolactin enhances the utilization of lipoproteins which carry a substrate necessary for progesterone synthesis. Likewise, Rajkumar *et al.* (1987) found that prolactin enhanced heparin-releasable surface binding of LDL to luteal cells in a dose-dependent manner; the maximal effect on LDL utilization was observed at a dose of 10 ng prolactin. These studies indicate that prolactin is a component of the luteotrophic complex in the second half of pregnancy in the pig.

At 1–3 days before parturition in the pig, prolactin begins to increase, reaching very high values (approximately 100 ng/ml plasma) at the time of delivery (Taverne *et al.*, 1979; Dusza & Krzymowska, 1981; Vale & Wagner, 1981; Kendall *et al.*, 1982). Taverne *et al.* (1982) suggested that PGF-2 $\alpha$  may be a factor which evokes the rise in prolactin concentrations in the periparturient pig much the same as administration of PGF-2 $\alpha$  to pregnant animals increases the concentration of prolactin. Bromocriptine administration did not interfere with delivery but lactation was blocked (Taverne *et al.*, 1982). The results of these studies indicate that the rise in prolactin concentrations in the preparturient period in pigs is important for the onset of lactation.

The relationship between prolactin and relaxin in the pig before parturition is also interesting although not entirely understood. In the preparturient period, Kendall *et al.* (1982) observed a close relation between secretion of prolactin and relaxin. Felder *et al.* (1988) administered prolactin 4 times daily at a dose 2.0 mg/day from Day 110 to Day 120 after mating in sows. The pre-partum relaxin peak was higher ( $P < 0.001$ ) in prolactin-treated animals in comparison with the saline-treated group and relaxin dropped to basal concentrations 1 day later in gilts receiving prolactin than in controls. Pregnancy duration was also lengthened by 1 day. The results of this study indicate an important effect of prolactin on relaxin secretion by ageing corpora lutea in late pregnant gilts.

### Prolactin and lactational infertility

During lactation in pigs decreased activity of the ovary is observed. Morphological and endocrinological studies revealed that growth of ovarian follicles is limited during lactation (for review see Britt *et al.*, 1985). In pigs prolactin concentrations are enhanced throughout the entire lactational period. Our own studies (for review see Dusza *et al.*, 1987) showed that very high prolactin concentrations at the beginning of lactation gradually fall as lactation proceeds but are still much higher than the basal concentrations observed during the oestrous cycle. At about 4–6 h after weaning, prolactin concentrations decrease markedly. Foxcroft *et al.* (1987) observed a dramatic decline in prolactin in 9 of 10 sows after weaning.

To study the role of prolactin in lactational infertility in sows we administered exogenous prolactin i.v. from immediately after weaning until occurrence of oestrus (Dusza *et al.*, 1984). Prolactin administration did not have any influence on plasma LH concentration and oestrus and a preovulatory LH surge occurred in all experimental animals (Fig. 5). Concomitantly a decrease in oestradiol-17 $\beta$  concentration occurred on the 2nd day after weaning and the exogenous prolactin reduced progesterone secretion by the newly formed corpora lutea in these sows. Oxytocin administration under a similar experimental schedule did not change LH and steroid hormone secretion (Kotwica *et al.*, 1984). However, the combined administration of prolactin and oxytocin resulted in a failure to produce a preovulatory surge in 3 of 10 experimental sows and changes in the oestradiol-17 $\beta$ , progesterone and testosterone profiles in 5 of 10 animals. Booman *et al.* (1982) treated sows throughout a 24-h period after weaning with prolactin and using more frequent

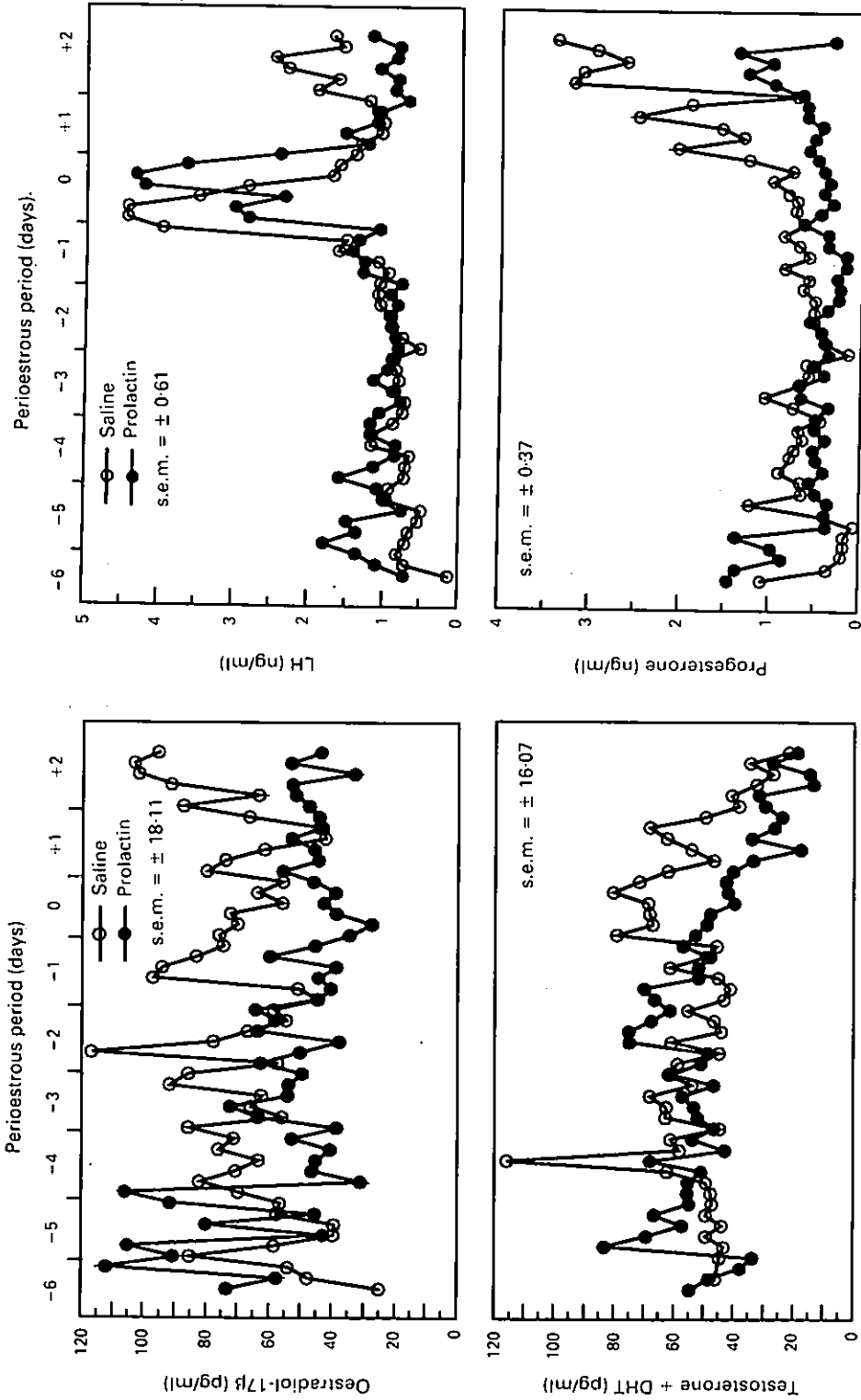


Fig. 5. Peripheral plasma concentrations of oestradiol-17β, LH, testosterone plus 5α-dihydrotestosterone, and progesterone in sows after saline (N = 5) or 0.125 mg prolactin (N = 5) every 2 h from weaning to the end of oestrus.

sampling found that mean plasma LH concentration, basal LH concentration and frequency of LH pulses were significantly lowered when compared with those of animals infused with saline, while prolactin did not influence the mean height of LH pulses. In some experimental situations, therefore, prolactin appears to inhibit LH secretion as well as ovarian steroidogenesis. Further evidence for an inverse relationship between plasma prolactin and LH concentrations was presented by Van de Wiel *et al.* (1985).

In conclusion, there is abundant evidence that prolactin has an influence on ovarian function during different physiological stages. However, the currently available data do not provide sufficient support for development of a general theory explaining the complete role of prolactin in the regulation of ovarian function. Further studies involving the combination of prolactin with other protein hormones and its interaction with the various ovarian growth factors (FGF, IGF-I, IGF-II and TGF) will continue to provide interesting avenues of research.

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