Follicular administration of a cyclo-oxygenase inhibitor can prevent oocyte release without alteration of normal luteal function in rhesus monkeys

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BACKGROUND: Prostaglandins (PG), produced by the follicle just before ovulation, appear to act locally to promote follicle rupture and oocyte release. METHODS: To determine whether administration of PG synthesis inhibitor directly into the primate follicle would prevent ovulatory events, serum estradiol was used to predict the day of the ovulatory LH surge in rhesus monkeys. On the day before or the day of the LH surge, vehicle (n = 9), the PG synthesis inhibitor indomethacin (10^-6 or 10^-5 mol/l final concentration; n = 8), or 10^-5 mol/l indomethacin + 1 µg/ml PGE2 (n = 3) was injected into the follicular fluid of the pre-ovulatory follicle. In some animals, luteal phase estrogen and progesterone were measured in daily serum samples. Other animals were ovariectomized 3 days after follicle injection; ovaries were examined for verification of follicle rupture and the absence of oocytes in vehicle-injected follicles (n = 3). Trapped oocytes were observed in 4/8 indomethacin-injected follicles, though several ovaries with trapped oocytes had experienced follicle rupture. Oocytes were not detected in the ruptured, luteinizing follicles from indomethacin + PGE2-injected monkeys (n = 3). CONCLUSIONS: Follicular administration of indomethacin can prevent oocyte release without inhibition of follicle rupture or disruption of subsequent luteal function. The ability of PGE2 to prevent indomethacin-induced ovulatory failure suggests a critical role for locally produced PGE2 in the process of oocyte release in primates.

Key words: follicle rupture/ovary/ovulation/prostaglandin

Introduction

The ovulatory surge of LH initiates a cascade of events leading to follicle rupture, oocyte release, and luteinization of the follicle wall. Prostaglandins (PG) have been proposed as essential intraovarian mediators of the ovulatory LH surge. The ovulatory gonadotrophin surge induces the expression of the PG synthetic enzyme cyclo-oxygenase (COX) isoform COX-2, but not the closely related isoform COX-1, in granulosa cells of the ovulatory follicle in a variety of mammalian species (Wong and Richards, 1991; Sirois, 1994; Sirois and Dore, 1997) including monkeys (Duffy and Stouffer, 2001). In each of these species, increased COX-2 expression is followed by increased follicular fluid levels of PG of the E and F series just before the expected time of ovulation, supporting a role for locally produced PG as mediators of ovulatory processes.

Systemic administration of COX inhibitors blocks ovulatory events in various species, including primates. Administration of general COX inhibitors to monkeys (Wallach et al., 1975) and women (Killick and Elstein, 1987) around the time of administration of the ovulatory dose of gonadotrophin can cause the development of luteinized, unruptured follicles (LUF). Recently, oral administration of a COX-2 selective inhibitor was shown to delay follicle rupture in women experiencing natural menstrual cycles (Pall et al., 2001). Minor or no disruption of subsequent luteal function was noted following administration of COX inhibitors around the time of ovulation in these studies (Killick and Elstein, 1987; Athansiou et al., 1996; Pall et al., 2001). These data indicate that, while PG may play an essential role in follicle rupture, they may not be required for luteinization of the follicle and normal luteal function.
The local action of PG within the follicle to mediate the ovulatory effects of the mid cycle gonadotrophin surge has been demonstrated for some mammalian species. Using perfused ovaries from rats (Mikuni et al., 1998) and rabbits (Zanagnolo et al., 1996), the ovulatory effects of gonadotrophin were inhibited by administration of a COX inhibitor but could be restored by co-administration of the COX inhibitor and PGE2 or PGF2α. However, an essential role for locally produced PG in mediating ovulatory processes has not been studied in primates. In addition, studies examining the role of PG in ovulatory events in monkeys and women have relied on visual assessment of a breach of the ovarian surface or ultrasound assessment of follicle size as indicators of follicle rupture (Killick and Elstein, 1987; Athansiou et al., 1996; Pall et al., 2001); oocyte release was not confirmed. The current studies were designed to determine if locally produced PG are necessary for ovulatory events in a primate species, the rhesus macaque. Vehicle or the COX inhibitor indomethacin was injected directly into large, spontaneously developed follicles near the time of the ovulatory LH surge. Injected ovaries were subsequently removed to determine if follicle rupture and oocyte release occurred. Co-injection of indomethacin and PGE2 was performed on additional animals to determine if replacement of PGE2 could restore indomethacin-inhibited ovulatory function.

Materials and methods

Animal protocols
The general care and housing of rhesus monkeys (Macaca mulatta) at the Oregon National Primate Research Center (ONPRC) were described previously (Molskness et al., 1987). Animal protocols and experiments were approved by the ONPRC Animal Care and Use Committee, and studies were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals. Adult females with regular menstrual cycles were checked daily for menstruation, and blood samples were obtained daily from non-anaesthetized monkeys by saphenous venipuncture from day 6 following the onset of menstruation. Serum was stored at −20°C. Serum estradiol and progesterone concentrations were determined by specific electrochemiluminescence assay using an Elecsys 2010 Clinical Assay Instrument (Roche Diagnostics, Indianapolis, IN, USA); intra- and inter-assay coefficients of variation (CV) did not exceed 10%. LH concentrations were determined by the mouse Leydig cell bioassay (Ellinwood and Resko, 1980) using monkey LH RP-1 as the standard (supplied by the NIH Hormone Distribution Program); intra- and inter-assay CV for the LH bioassay did not exceed 15%.

The follicular injection model used for administration of test compounds directly into the follicular fluid of the pre-ovulatory follicle in rhesus macaques has been previously described (Hazzard et al., 2002). Briefly, daily serum estradiol levels were used initially to predict the day of the ovulatory LH surge. The peak in serum LH concentrations is known to occur most often on the day of or the day after peak serum estradiol levels (Weick et al., 1973). On the day of or the day after the serum estradiol peak, an aseptic laparotomy was performed on the anaesthetized monkey to identify the ovary bearing the dominant follicle. A syringe with a 28 G needle and a very small hub volume, was loaded with 50 µl vehicle or test compound, and the needle of this syringe was inserted at the end of the ovary opposite to the follicle and into the antrum of the dominant follicle. An equal amount (50 µl) of follicular fluid was aspirated into the syringe, and preliminary experiments confirmed excellent mixing of the pre-loaded liquid and follicular fluid within the syringe. Without withdrawing the needle of the syringe from the follicle, 50 µl of follicular fluid mixed with vehicle or test compound was injected back into the follicle, restoring the original volume of the follicle. The needle of the syringe was then withdrawn from the ovary. Careful placement of the syringe needle resulted in minimal leakage from the injected follicle, and a sterile cotton swab was placed over the injection site for several minutes to ensure closure. Previous studies employing follicle aspirations determined that the volume of follicular fluid contained within the ovulatory follicle in macaques is ~200 µl; therefore, the final concentration of vehicle or test compound within the follicle following injection was calculated based on this estimate. Final concentrations of test compounds in macaque follicles were 10⁻⁷ and 10⁻⁵ mol/l indomethacin (Sigma Chemical Co., St Louis, MO, USA) in a vehicle of dimethylsulphoxide (DMSO, <0.02% final concentration; Sigma) and 1 µg/ml PGE2 (Cayman Chemical, Ann Arbor, MI, USA) in a vehicle of ethanol (0.1% final concentration). All vehicle and test compounds were diluted in phosphate-buffered saline, pH 7.4.

For all animals, an aseptic laparoscopic surgery was performed 3 days after follicle injection. In some experiments, the appearance of the ovulatory stigmata was recorded by digital video, and animals continued to be bled daily for determination of serum estradiol and progesterone. In these experiments, the date of first menstruation was also recorded. In additional experiments, injected ovaries were removed 3 days after follicle injection at laparoscopic surgery. These ovaries were fixed in 4% paraformaldehyde, embedded in paraffin, and serial sectioned at 5 µm; every fifth section was stained with haemotoxylin and eosin. The presence of a rupture site as well as an oocyte within the injected follicle was determined by examination of each stained section.

Data analysis
Analyses of serum LH and steroid concentrations were performed using a two-way analysis of variance (ANOVA) with one repeated measure, followed by Newman–Keuls’ test when indicated. All data were assessed for heterogeneity of variance using Bartlett’s test and log-transformed when necessary before ANOVA. In all studies where serum LH, estradiol and progesterone levels were determined during the ovulatory period and luteal phase of the menstrual cycle, animals were administered follicular injection of vehicle during one menstrual cycle. In a subsequent menstrual cycle, these animals received follicular injection of a test compound. In this way, each animal served as its own control, and all serum hormone data were analysed using repeated measures to compare control and treatment cycles within animal. The interval from the LH surge to the onset of menstruation (i.e. length of the luteal phase) was analysed using paired t-test. Detection of oocytes in follicles was compared using χ²-test with correction for small sample size (Goldstein, 1964). Data are presented as mean ± SEM, and significance was assumed at P < 0.05.

Results

Hormonal patterns in treatment groups
To determine if monkeys experienced normal menstrual cycles following follicular injection of vehicle (0.02% DMSO, n = 6), daily serum samples were assayed for estradiol, LH, and progesterone. Follicular injections were performed within 1 day of the peak day of pre-ovulatory estradiol levels (Figure 1). During these vehicle injection cycles, monkeys
Cyclooxygenase inhibitor blocks oocyte release

Figure 1. Serum estradiol and progesterone concentrations before and after follicle injection. Follicle injection was performed on the day before or on the day of peak estradiol levels, as indicated by the shaded box. Follicles were injected with vehicle (closed squares) or indomethacin at final follicular concentrations of $10^{-6}$ mol/l (open circles) or $10^{-5}$ mol/l (open triangles). Data are normalized to the peak day of LH for each animal (day 0). Day of first menstruation is indicated for animals receiving follicle injections of vehicle (M) and indomethacin at final follicular concentrations of $10^{-6}$ mol/l (M) or $10^{-5}$ mol/l (m). Serum progesterone concentrations were different between vehicle and $10^{-5}$ mol/l indomethacin groups only on day 4, as denoted by the asterisk ($P < 0.05$). Data are presented as mean ± SEM.

experienced ovulatory LH surges with peak levels of 232 ± 44 ng/ml on the day of or the day after follicular injection. Serum estradiol was detected throughout the luteal phase (Figure 1), and levels were consistent with normal luteal function. Progesterone concentrations were low on the day after the LH peak, rose to peak levels of 2.44 ± 1.01 ng/ml on day 9 after the LH peak, and fell to low levels prior to the onset of menstruation (Figure 1). The average day of first menstruation was day 17 ± 0.8 after the LH peak. These data are similar to previous reports of normal luteal function in rhesus monkeys (Duffy et al., 1994). Similar data were obtained when a monkey received follicular injection of a vehicle of 0.1% ethanol ($n = 1$, data not shown).

During subsequent menstrual cycles, these same animals received follicular injection of the cyclooxygenase inhibitor indomethacin at final follicular concentrations of $10^{-6}$ mol/l ($n = 4$) and $10^{-5}$ mol/l ($n = 4$). In all animals, follicular injections were performed within 1 day of peak pre-ovulatory estradiol levels (Figure 1), and monkeys experienced ovulatory LH surges with peak concentrations of 259 ± 58 ng/ml ($10^{-6}$ mol/l) and 383 ± 108 ng/ml ($10^{-5}$ mol/l) on the day of or the day after follicular injection (Figure 1). In both $10^{-6}$
and $10^{-5}$ mol/l indomethacin treatment cycles, serum levels of LH were not different from the levels of these hormones measured during vehicle injection cycles. Serum steroids were very similar between vehicle- and indomethacin-treated monkeys during the luteal phase following follicular injection. Serum progesterone concentrations were not different between vehicle- and indomethacin-injected monkeys, with the exception of luteal day 4, when progesterone levels were lower in monkeys receiving $10^{-5}$ mol/l indomethacin when compared with vehicle-treated animals ($P < 0.05$). Peak progesterone levels were achieved between luteal days 8–10 in all groups (Figure 1). Estradiol levels were not different between vehicle- and indomethacin-treated monkeys during the preovulatory peak or the luteal phase (Figure 1). Day of first menstruation was not different between indomethacin- and vehicle-injected cycles when data were compared within animal (Figure 1).

**Ovarian morphology**

When laparoscopic evaluations of the ovarian surface were performed 3 days after follicular injection, all vehicle-treated monkeys showed ovulatory stigmata on the injected ovaries (Figure 2A; $n = 6$). These ovulatory stigmata featured red, luteinizing tissue protruding through an opening in the ovarian surface; they were often observed leaking bloody fluid. Histological examination of sections of vehicle-injected ovaries (Figure 2F; $n = 3$) showed luteinizing granulosa cells with notable stromal infoldings, typical of luteinizing follicles 2–3 days after exposure to peak LH levels. An ovulatory canal connected the collapsing follicular antrum with the exterior of the ovary, and luteinizing tissue protruded through a breach in the ovarian surface epithelium (Figure 2D).

Injection of ovaries with indomethacin altered the structure of the dominant follicle. Laparoscopic evaluation of the ovarian surface 3 days after follicle injection showed that three out of four ovaries injected with $10^{-6}$ mol/l indomethacin and one out of four ovaries injected with $10^{-5}$ mol/l indomethacin (data not shown) had ovulatory stigmata similar to those observed in vehicle-injected animals. Ovulatory stigmata smaller than those observed in control animals were seen in one animal following injection with $10^{-6}$ mol/l indomethacin (data not shown) and two animals after injection with $10^{-5}$ mol/l indomethacin (Figure 2B). These small rupture sites had smaller breaches in the ovarian surface epithelium and lacked the protruding luteinizing tissue characteristic of the ovulatory stigmata observed in vehicle-treated monkeys (Figure 2E). In one ovary treated with $10^{-5}$ mol/l indomethacin, no breach in the surface epithelium was identified (data not shown). Upon examination of the histological ovarian sections, all ovaries injected with $10^{-6}$ mol/l ($n = 4$) or $10^{-5}$ mol/l ($n = 4$) indomethacin showed luteinizing granulosa cells and stromal infoldings similar to vehicle-injected ovaries (Figure 2G).

To determine if PG replacement could reverse the effects of indomethacin treatment on follicle structure, additional animals received follicular injection to achieve final concentrations of $10^{-5}$ mol/l indomethacin + $1 \mu$g/ml PGE$_2$ within the follicular fluid, followed by removal of the ovary 3 days after injection as described above ($n = 3$). Ovaries injected with indomethacin + PGE$_2$ formed large protruding stigmata similar to those observed on vehicle-injected ovaries, except that these structures appeared paler in colour and less vascular (Figure 2C). Examination of ovarian tissue sections showed well-luteinized follicles (Figure 2H). These follicles contained stromal infoldings and luteinizing granulosa cells similar to those seen in vehicle- and indomethacin-injected ovaries.

**Oocyte detection**

Serial sections of each ovary collected were examined for the presence of an oocyte trapped within the luteinizing follicle. Oocytes were never observed within the luteinizing ovulatory follicle of vehicle-injected ovaries (Table I). However, oocytes were identified within the luteinizing follicles of 50% of ovaries injected with either $10^{-6}$ or $10^{-5}$ mol/l indomethacin (Table I; $P < 0.05$ when comparing all indomethacin-injected ovaries versus vehicle). The retained oocytes were not detached from the follicle wall but were surrounded by luteinizing granulosa cells and encased within the developing corpus luteum (Figure 2I). Oocytes were never observed within or near the antrum of the luteinizing follicles. One of these four trapped oocytes was found within the $10^{-5}$ mol/l indomethacin-injected ovary lacking a breach in the ovarian surface epithelium. However, three oocytes were found within indomethacin-injected follicles with rupture sites. No oocytes were located within follicles injected with indomethacin + PGE$_2$ (Table I; $n = 3$).

**Discussion**

This is the first study to demonstrate that local administration of a COX inhibitor to the follicle just before the expected time of ovulation can prevent oocyte release in primates. Oocytes were observed in half of all indomethacin-injected follicles examined. These retained oocytes were trapped within the luteinizing granulosa cells of the developing corpus luteum. Oocytes were never seen in vehicle-injected ovaries, indicating that indomethacin treatment was responsible for the observed retention of the oocyte. Restoration of ovulatory function by co-injection of indomethacin and PGE$_2$ supports the hypothesis that COX-2-mediated synthesis of ovarian PGE$_2$ is essential for oocyte release in primates.

Systemic administration of COX inhibitors, including indomethacin and others, to monkeys and women demonstrated that these drugs can cause delayed ovulation (Hedin et al., 1987; Pall et al., 2001), failure of the follicle to rupture (Hedin et al., 1987; Killick and Elstein, 1987), and infertility (Akiil et al., 1996; Mendonca et al., 2000). In these studies, methods including ultrasound or visual inspection of the ovaries were used to determine if COX inhibitor treatment resulted in LUF or delayed ovulation; the location of the oocyte was not determined. In the present study, ovulation failure was assessed by direct examination of ovarian tissue sections to determine if an oocyte was present within the luteinizing follicle. The absence of an identifiable oocyte occurred in 50% of indomethacin-injected ovaries and none of the vehicle-injected ovaries. Failure to detect oocytes in indomethacin-injected ovaries probably reflects oocyte release but could also result from oocyte atresia. In most cases, indomethacin...
Figure 2. Ovarian morphology and trapped oocytes after follicular injection. Follicles were injected with vehicle (A, D, F), $10^{-6}$ mol/l indomethacin (I), $10^{-5}$ mol/l indomethacin (B, E, G), or $10^{-5}$ mol/l indomethacin + prostaglandin E$_2$ (PGE$_2$) (C, H). Three days after follicle injection, the ovary was observed during laparoscopic surgery (A–C). Some ovaries were removed 3 days after follicle injection, and serial sections were stained with haematoxylin and eosin (D–I). In A–C, the ovulatory stigmata is indicated by an arrow; the ovulatory opening in D and E is indicated by an arrow. Histological examination of ovarian sections (D–H) shows the presence of luteinizing granulosa cells (lgc), stromal infoldings of the developing corpus luteum (st), the ovulatory canal (oc), and the ovarian surface epithelium (se). Trapped oocytes were observed within four out of eight indomethacin-injected follicles (I). The oocyte (arrow) of the injected follicle is surrounded by luteinizing granulosa cells (lgc); the oocyte (asterisk) of a neighbouring secondary follicle surrounded by ovarian stroma (st) is also shown. (D, E) Bar = 200 µm; (F–H) bar = 40 µm; (I) bar = 100 µm.

| Table 1. Indomethacin and prostaglandin E$_2$ (PGE$_2$) effect on oocyte release |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Treatment group                | Indomethacin $10^{-6}$ mol/l    | Indomethacin $10^{-5}$ mol/l    | Indomethacin $10^{-5}$ mol/l + PGE$_2$ |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Vehicle                         | 0/3                             | 2/4                             | 2/4                             | 0/3                             |
| Trapped oocytes/no. of injected follicles |                                  |                                 |                                 |                                 |

Follicles were injected with vehicle or test compound(s) ($n = 3–4$ /group) as indicated and removed 3 days after injection. Serial sections of ovaries were stained with haematoxylin and eosin, and every fifth section was examined as described in Materials and methods. Number of trapped oocytes was greater in indomethacin-injected follicles ($10^{-5}$ and $10^{-6}$ mol/l treatment groups combined) when compared with vehicle-injected follicles by $\chi^2$-analysis ($P < 0.05$).
injection did not eliminate the formation of the ovulatory opening; only one luteinized, unruptured follicle was observed. Data from previous studies, along with those presented here, indicate that a variety of ovulatory defects can result from COX inhibitor administration. Factors such as the specific inhibitor used, dosage, method of administration, or timing of administration relative to the time of the ovulatory gonadotropin surge may be responsible for these differences in ovulatory defects. Data from the present study demonstrate that follicle rupture does not ensure oocyte release and support the use of direct measures of ovulatory success, such as localization of the oocyte within the reproductive tract, in future studies.

Indomethacin administered by follicular injection probably prevents oocyte release by inhibition of ovarian PG synthesis. The best-characterized action of indomethacin is the inhibition of COX activity, but indomethacin can also affect other cellular functions (Tegeder et al., 2001). For this reason, additional animals received follicle injection of indomethacin plus PGE2 at levels similar to the peak concentration of PGE2 measured in monkey follicular fluid 4 h before the expected time of ovulation (Duffy and Stouffer, 2001). In the present study, follicle injection with indomethacin and PGE2 restored oocyte release when compared with injection of indomethacin alone. Studies using knockout mice demonstrated that mice lacking COX-2 expression have defects in ovulation (Lim et al., 1997), and treatment of these mice with PGE2 restored ovulatory function (Davis et al., 1999). An essential role for the PGE receptor subtype EP2 in cumulus expansion has been demonstrated using mice lacking expression of this receptor (Hizaki et al., 1999). In the present study, oocytes were observed surrounded by luteinizing granulosa cells within indomethacin-treated ovaries, suggesting that failure of cumulus expansion may have prevented the oocyte–cumulus complex from detaching from the follicle wall in these ovaries. These data are consistent with a role for PGE2 in cumulus expansion in primates as well as rodent species, though additional studies will be required to fully address this question.

Follicular injection of indomethacin does not appear to alter some essential ovarian processes including luteal formation, luteal function, or timely luteal regression. Luteinizing granulosa cells streaming into the antrum of the follicle and stromal infoldings were observed in serial sections of ovaries injected with vehicle, indomethacin, and indomethacin + PGE2, suggesting that formation of the corpus luteum proceeded normally following all treatments. In addition, little disruption of luteal function was noted following indomethacin injection. Few differences in circulating estrogen and progesterone between indomethacin- and vehicle-injected animals during the luteal phase suggests that inhibition of PG synthesis during the ovulatory interval does not prevent processes necessary for luteal formation and subsequent steroidogenic function, consistent with previous reports of studies performed in women (Killick and Elstein, 1987; Athansiou et al., 1996; Pall et al., 2001). However, other studies show that manipulation of luteal PG concentrations do alter luteal function and life span in primates (Auletta and Flint, 1988). Additional studies will be required to determine if intraovarian administration of COX inhibitors throughout the entire menstrual cycle alters ovarian function and/or menstrual cyclicity.

Because the cells of the primate ovulatory follicle express COX-2, but not COX-1 (Duffy and Stouffer, 2001), indomethacin most likely blocks oocyte release by inhibition of ovarian COX-2 activity. However, the specific mechanism(s) by which indomethacin prevents normal ovulatory function in primates is unknown. Studies using the isolated perfused ovary model demonstrated that infusion of the COX-2 selective inhibitor NS-398 prevented follicle rupture in rats (Mikuni et al., 1998), and oral administration of the COX-2 selective inhibitor rofecoxib delayed follicle rupture in women (Pall et al., 2001), supporting the hypothesis that ovarian COX-2 activity is essential for normal ovulation to occur. The poor solubility and high IC50 of NS-398 when compared with indomethacin has hindered our efforts to compare the ability of these COX inhibitors when injected into the monkey follicle in advance of the expected time of follicle rupture (D.M. Duffy and R.L. Stouffer, unpublished data). Based on our current studies, further studies are warranted using isoform selective COX inhibitors to evaluate the roles of COX-1 and COX-2 in ovulatory events in primates.

The data presented here are consistent with the hypothesis that inhibition of ovarian COX-2 activity and subsequent prevention of PGE2-regulated cumulus expansion results in the trapping of the oocyte within the granulosa cells of the luteinizing follicle, resulting in the failure to ovulate. PG may be involved in the formation of the ovulatory stigma, but follicular PG such as PGE2 do not appear to be essential for luteinization of the follicle or subsequent luteal function. Enhanced understanding of the mechanism by which PGE2 and possibly other PG mediate follicle rupture and oocyte release in monkeys and women may lead to improved treatment for infertility due to ovulation failure. In addition, inhibition of PG production may form the basis for the development of novel contraceptive strategies.

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