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PROSTAGLANDIN F2ALPHA AND OXYTOCIN INTERACTIONS IN OVARIAN AND UTERINE FUNCTION

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Summary—The oxytocin–neurophysin gene is expressed in several nontraditional sites within the endocrine system. In the ovary its expression in the corpora lutea is initiated by ovulation. Ovarian oxytocin concentrations reach maximal levels around day 11 of luteal cycle and fall to a nadir at estrus. PGF2alpha has the capacity to release oxytocin from the corpus luteum, and oxytocin in turn releases PGF2alpha from the uterine endometrium or decidua. This positive feedback loop between the ovary and the uterus ensures the completion of luteolysis in species that depend on the presence of the uterus for the termination of luteal lifespan. Immunization against oxytocin has been shown to disrupt this loop, resulting in much-prolonged luteal cycles. In primates and other species in which luteal life span is independent of the uterus, an oxytocin PGF2alpha interaction may take place within the ovary itself.

At parturition a related interaction takes place which ensures the expulsion of the fetus and placenta in an orderly manner. Oxytocin of both pituitary and ovarian origin reaches the uterus via its blood supply and binds to two types of receptors: one on myometrial cells, the occupation of which initiates contractions, and the other on decidual cells, the occupation of which initiates prostaglandin generation. This prostaglandin diffuses into the adjacent myometrium and augments the oxytocin-induced contractions. In conjunction with a direct softening effect by prostaglandins on the cervix the augmented contractions achieve the force needed to dilate the cervix and expel the fetus. An additional source of oxytocin during labor may be the placenta, another non-traditional site for the occurrence of oxytocin.

INTRODUCTION

Prostaglandins F2alpha and E2 play an important role in the cyclic events that characterize female reproductive function. PGF2alpha mediates the irreversible regressive changes that lead to follicular rupture at ovulation, the demise of the corpus luteum at luteolysis, the shedding of the endometrium at menstruation and the expulsion of the products of conception at parturition. Although ovarian hormones influence the prostaglandin synthetase activity in the tissues of the reproductive tract, they do not seem to have a direct effect on the release of prostaglandins. *In vivo*, the release of prostaglandins is regulated by a balance of inhibitory and stimulatory factors of both intracellular and extracellular origin; some of the inhibitors were discussed by Dr Hirata at this symposium. Several peptides and biogenic amines have been found to stimulate prostaglandin release from various tissues; these include epinephrine, histamine, bradykinin, interleukin-2, various growth factors, angiotensin I and II and the neurohypophysial hormones. For the functions of the female reproductive tract the interaction of oxytocin and prostaglandin is of special interest. Luteolysis, at least in some species, and parturition depend on this interaction which takes place on several levels: oxytocin stimulates prostaglandin release, PGF2-alpha stimulates oxytocin release, and a mutual modulation of end-organ responses has also been observed.

PROSTAGLANDIN AND OXYTOCIN INTERACTION IN OVARIAN FUNCTION

The recent discovery that the genes coding for the synthesis of neurohypophysial hormones are expressed in endocrine organs outside the brain [1, 2] suggests that these hormones may have important functions in tissues other than their traditional target organs, the kidney, the uterus and the mammary gland. The ovary has so far with certainty been shown to be a site of synthesis of both these hormones [1, 2]; in addition, testis [3], adrenal [3–5] and placenta [6–8] have been shown to contain oxytocin in amounts so large that it is unlikely to be taken up from the circulation.

In the ovary, oxytocin is located in secretory granules in the large luteal cells [9, 10]. Ovarian content and concentration of oxytocin varies cyclically. Table 1 shows values for bovine corpus luteum (Fields and Fuchs, unpublished observations). Both the content and the concentration of oxytocin rise in the early phases of luteal development and reach maximal values around day 11, when the content is comparable to pituitary content, then declining to very low levels at estrus. Ovulation triggers the expression of the oxytocin gene in the bovine ovary [11]. Species in which the uterus regulates the lifespan of the corpus luteum such as the cow [6, 12], ewe [13], and sow [14] have high ovarian oxytocin concentrations whereas species such as the primates [15–17] in which the influence

Table 1. Oxytocin in bovine corpus luteum during the estrous cycle (values are medians)

Day	wt, g	OT pmol/g	OT pmol/gland	n
0	1.85	3.2	5.8	2
1	3.31	6.5	21.3	1
3	0.55	119	67.6	2
7	3.05	384	1181	2
11	4.75	702	3688	2
14	4.65	225	1048	3
17	2.64	13.0	34.3	3
19	3.08	17.5	46.3	5

of the uterus on corpus luteum function is negligible [18], have considerably lower ovarian oxytocin levels.

PGF2alpha has the capacity to release oxytocin from the corpus luteum [9, 13]. Oxytocin concentrations in the ovarian vein rise to very high levels, about 600 pg/ml, in response to an intra-arterial injection of a PGF2alpha or its synthetic analogs whereas jugular venous and ovarian arterial levels rise much less. The much higher arteriovenous difference in the ovarian vein than in the jugular vein demonstrates the ovarian origin of the hormone [19]. Oxytocin in turn has the capacity to release PGF2alpha from the uterus of many species. In the nonpregnant ewe the capacity of oxytocin to release PGF2alpha varies during the cycle. About 100-fold greater amounts of PGF2alpha are released in late luteal phase in response to a given dose of oxytocin than in the early phase [20]. The increased response to oxytocin parallels the increase in uterine oxytocin receptors [20]. Both the myometrium and the endometrium of the ewe possess oxytocin receptors and in the nonpregnant ewe the endometrial oxytocin receptor concentration exceeds that in the myometrium in all cycle stages. The endometrium has a higher capacity to produce PGF2alpha than the myometrium, which produces predominantly prostacyclin [21, 22], and the oxytocin-induced PGF2alpha release from the nonpregnant uterus probably originates in the endometrium.

The importance of the oxytocin-induced release of PGF2alpha for luteolysis is indicated by the fact that heifers or ewes that are actively immunized against oxytocin show much-prolonged luteal cycles [23–25] during which estrus can be induced by administration of exogenous PGF2alpha. In normal animals, estrous cycles can be shortened and luteolysis induced by repeated injections of oxytocin [26–28], but in hysterectomized animals oxytocin injections are without effect on luteal function, indicating that a uterine factor is essential for the luteolytic effect of oxytocin in these species. In early pregnancy the PGF2alpha-releasing capacity of oxytocin is strongly suppressed [29]; proteins secreted by the early embryo produce this antiluteolytic effect [30], which thus may be the signal for maternal recognition of pregnancy.

Ovarian oxytocin may have another, direct effect on luteal function. According to some authors, low concentrations of oxytocin stimulate while high concentrations inhibit progesterone production in luteal cells *in vitro* [31, 32]. Conflicting results have been obtained by others [33, 34], so this aspect of oxytocin action remains controversial.

In primates and other species in which uterine factors are not needed for the regulation of luteal function [18], ovarian oxytocin may act in a paracrine fashion to stimulate intraovarian PGF2alpha release which in turn acts on the luteal cells to suppress progesterone production. Auletta *et al.* [35] have recently demonstrated that oxytocin infused directly into the corpus luteum suppresses progesterone secretion and significantly shortens the luteal lifespan in rhesus monkeys. Likewise, intraluteal but not systemic PGF2alpha infusions cause luteolysis in this species [36]. The paracrine regulation of luteal function in primates may require the additional interaction of PGF2alpha with catecholamines. Noradrenaline and PGF2alpha are ineffective in suppressing either progesterone or cAMP production in human luteal cells *in vitro* when added separately but have a strong inhibitory effect when given together [37]. There is very substantial ingrowth of noradrenergic nerves into the human corpus luteum during the luteal cycle [38], which may explain why the corpus luteum is responsive to PGF2alpha-induced luteolysis only in the late luteal phase not only in primates but also in other species [36, 39, 40].

PROSTAGLANDIN AND OXYTOCIN INTERACTION IN PARTURITION

In regard to parturition, it has long been known that both oxytocin and prostaglandins are essential for the process of labor. Inhibition of oxytocin release by ethanol [41] delays the onset of labor [42] and stops ongoing labor in its early phases [43]. Antagonists of oxytocin action prolong gestation and stop labor in experimental animals [44]. Administration of cyclooxygenase inhibitors also delays the onset of labor and stops preterm labor [45–47]. Administration of oxytocin reverses the action of ethanol [48] while PGF2alpha or PGE2 reverse the action of indomethacin and other cyclooxygenase inhibitors.

Several observations support the view that in pregnant women oxytocin is of greatest importance for the initiation of labor whereas PGF2alpha is required to maintain labor and dilate the cervix. According to this view, oxytocin has a dual action on the uterus—it initiates uterine contractions through its receptors on myometrial cells and initiates the generation of PGF2alpha through its receptors in the decidua [49]. The evidence for this view is reviewed here.

Table 2. Myometrial oxytocin receptor concentrations at various stages of gestation in women with normal pregnancy (For comparison, values in non-pregnant myometria are also shown.)

		Oxytocin receptors (fmol/mg) DNA		
	n	Lognormal mean	Median	Intercentile range
Non-pregnant patients	15	20.7	18.7	11.3–40
Pregnant, 13–17 wks	5	128	110	65–417
Pregnant, 37–41 wks	16	1620	1140	1081–2490
Early labor, 38–41 wks (repeat C.S., cervix ≤ 4 cm)	10	3885	3550	3090–4240
Preterm labor, 28–36 wks	8	2896	2870	2468–3628
Failed induction, 38–43.5 wks	8	908	836	431–1774

P values were <0.001 except between groups 3 and 4 $P < 0.025$ and between groups 4 and 5 $P > 0.05$. (Adapted from [51])

(1) While no changes in the levels of the various steroidal regulatory factors have been detected before the onset of labor in women either in the circulation or in the various intrauterine tissues [50], the concentration of oxytocin receptors in the myometrium rises significantly [49, 51] (Table 2). The oxytocin receptor concentrations at term are about 80 to 100 times higher than nonpregnant levels and a further 2–3-fold rise occurs at the time of labor. This increase lowers the threshold for stimulation of uterine contractions by oxytocin to levels normally seen in the plasma of late pregnant women. Infusions of 1–3 mU/min oxytocin are sufficient to stimulate uterine contractions in pregnant women at term but usually not before term. During such infusions, plasma oxytocin levels are not significantly raised over those seen in normal pregnant women before the onset of labor [52] (Table 3). Infusion rates of 4–6 mU/min are commonly used to induce labor near term; they result in plasma oxytocin levels that are similar to the average plasma oxytocin concentrations observed during the first stage of labor.

(2) In contrast to the oxytocin receptors, myometrial prostaglandin E and F receptor concentrations in pregnant women do not rise before or during labor, and remain at nonpregnant levels throughout gestation [53].

(3) The plasma levels of PGF2alpha metabolite, which in other species reflect the production of PGF2alpha in the uterus, do not rise significantly until labor is well under way, and then increase rapidly in parallel with cervical dilatation [54, 55]. Amniotic prostaglandins behave similarly with no significant rise before the onset of labor but a marked rise after the cervix is dilated to 4 cm or more [56]. Peripheral levels may not, however, reflect small changes in the local production rates. We have therefore measured prostaglandin concentrations in the uterine venous effluent and compared these values with simultaneously taken peripheral venous samples (Table 4). PGE or F levels in uterine venous plasma were not raised over peripheral venous levels before the onset of labor or in early labor. In advanced labor, on the other hand, both at term and preterm, PGF2alpha levels in the uterine vein were considerably higher than in the peripheral blood, indicating that the increased uterine production of this prostanoid during labor is of uterine origin also in women.

(4) Human uterine decidua possesses oxytocin receptors that have the same characteristics as

Table 3. Plasma oxytocin levels in spontaneous and oxytocin-induced labor at term

Spontaneous labor			Oxytocin-induced labor		
Cervix (cm)	Oxytocin (μU/ml)	*n*	Infusion rate (mU/min)	Oxytocin (μU/ml)	*n*
Before <2	11.8 ± 1.84	16	Before	10.3 ± 2.9	15
<4	28.1 ± 4.5*	14	1–3	12.6 ± 3.8	8
4–6	27.6 ± 4.6*	13	4–6	29.2 ± 6.5*	12
7–9	25.6 ± 3.9	19	7–9	35.0 ± 5.9*	16
10	27.3 ± 2.1*	7	10–16	65.6 ± 13.5*	10

Measurements were made in serial samples obtained from 17 and 15 women, respectively; the results are arranged according to the cervical status or the infusion rate at the time of sampling.

Values are mean ± SEM. *Significantly different from values before the onset of labor. Adapted from [52] and [55].

Table 4. Uterine vein plasma prostaglandin concentrations in percentage of peripheral plasma values

	n	PGE (%)	PGF (%)	PGFM (%)
Term, no labor	6	93.9 ± 20.2	107.1 ± 21.2	113.0 ± 17.8
Term, labor	6	154 ± 11.7*	464 ± 197*	170 ± 55.3
Term, failed induction	6	119.6 ± 13.5	88.3 ± 19.4	109.3 ± 20.5
Preterm, labor	6	251 ± 75.5†	263 ± 67.8†	104 ± 10.5

*Difference from peripheral values significant, Wilcoxon paired sample test, $P < 0.05$.
†Difference from peripheral values significant, Student's t-test.

myometrial receptors and increase in parallel with them, reaching maximal values at the time of labor [49, 51] (Table 5). Since decidual cells are not contractile cells, the function of these receptors must differ from that in myometrial and myoepithelial cells. Decidua has considerable prostaglandin synthetase activity [57, 58]; it also has a high phospholipid concentration including phosphoinositol containing lipids and considerable diacyl glycerol lipase activity [59]. We have shown that decidual explants *in vitro* produce significantly more PGF2alpha and PGE2 in the presence of nanomolar concentrations of oxytocin than in its absence [60]. Amnion explants responded to oxytocin with a smaller increase in the production of PGF whereas myometrial prostaglandin production was not affected by oxytocin. We have not found specific oxytocin binding sites in amnion but recently a Japanese group reported finding specific oxytocin binding sites also in this tissue [61]. We assume that the oxytocin-induced stimulation of prostaglandin production in human decidua is receptor mediated. Vasopressin, which binds to the receptors with a much lower affinity, does not stimulate prostaglandin production in decidua nor in amnion (Rehnström and Fuchs, unpublished observations). Oxytocin stimulates prostaglandin F2alpha production also *in vivo*; the responses to oxytocin increases in parallel to decidual oxytocin receptor concentrations (Table 6). No effect was observed in nonpregnant women in response to 1-h-long oxytocin infusion of 80 mU/min. In midpregnancy, the effect of the same dose of oxytocin on plasma PGF2alpha metabolite levels was transient and not maintained throughout the entire infusion period, but at term a sustained PGF production in response to a much lower oxytocin infusion rate (4–6 mU) was observed (Table 6) (Fuchs, Rehnström and Toth, unpublished observations).

Table 6. Influence of 1-h oxytocin infusion on plasma PGFM levels in women

	n	Increase in plasma PGFM (pg/ml)	OT Receptors* (fmol/mg DNA)
Nonpregnant	7	11 ± 6.7	21.1
Midpregnant	7	35 ± 13.4	629
Term pregnant	7	126 ± 27.1	2940

OT was infused for 1 h at a rate of 80 mU/min to nonpregnant and midpregnant women, and at a rate of 4–6 mU to term pregnant women; mean ± SE.
*Values from Table 5, log normal means.

(5) Induction of labor with oxytocin is successful only when the infusion of oxytocin is associated

Table 5. Oxytocin receptors in decidua in pregnant women (for comparison, values in nonpregnant endometrium are also shown)

		Oxytocin receptors (fmol/mg DNA)		
Patients	n	Log normal mean	Median	Intercentile range
Nonpregnant, endometrium	11	21.0[a]	25.3	14.1–40.0
Pregnant, 13 weeks	1	629[b]	629	—
Pregnant, 28–36 weeks	8	1980[b,c]	1571	258–6327
Pregnant, 37–41 weeks	8	2940[c]	2660	1069–7280
Early labor, 38–41 weeks	2	3210[c]	3870	1710–6030
Preterm labor, 28–36 weeks	10	3030[c]	2277	855–6159
Failed induction, 41–43.5 weeks	3	305[b]	407	81–770

a, b, c: Values with different superscripts are significantly different from each other, $P < 0.05$.

with an increase in the production of PGF2alpha. We have found that plasma PGF metabolite levels always rise during successful induction of labor with oxytocin whereas in induction failures to PGF2alpha or only transient rise in PGFM is observed [62]. Decidual oxytocin receptor concentrations were found to be significantly lower in women in whom cesarean section was performed because of induction failure than in women in whom a repeat elective cesarean section was performed either in early spontaneous labor or at term (Table 5). This finding suggests that a critical concentration of oxytocin receptors may be required to initiate prostaglandin synthesis in the decidua. Another possibility that should be explored is that the coupling of oxytocin receptor occupancy to the prostaglandin synthetase complex requires the presence of a coupling protein in the cell membrane, the formation of translocation of which is regulated separately from the receptor and prostaglandin synthetase concentrations.

(6) The converse has also been observed, namely the apparent requirement for oxytocin in prostaglandin inductions. When PGE2 was applied locally around the cervical os to induce labor, plasma oxytocin and PGF2alpha metabolite levels rose in all induction successes whereas no rise was observed in induction failures [63].

MODULATION OF END-ORGAN RESPONSES

Prostaglandins E and F2alpha potentiate the uterine response to oxytocin [64–66] and lower the threshold for stimulation of myometrial activity by oxytocin [67]. According to a recent, preliminary report [61] this may be caused by an increase in the affinity of the oxytocin binding sites by PGF2alpha. Prostaglandins may also potentiate the response to oxytocic agents in general through a postulated enhancement of gap junction formation by prostaglandins [68], or by their inhibitory effect on the sarcolemmal Ca^{2+} extrusion pump [69]. Inhibition of this enzyme, Ca^{2+}-ATPase, increases intracellular free Ca^{2+} concentration and thus promotes contraction. PGE2 and PGF2alpha cause half-maximal inhibition of this enzyme at concentrations that have negligible effect on human myometrial contractions by themselves, between 1 and 10 ng/ml.

Oxytocin, on the other hand, acts to synchronize prostaglandin-induced contractions. This effect, which can be demonstrated with exogenous hormones (Fig. 1), could be of great importance under *in*

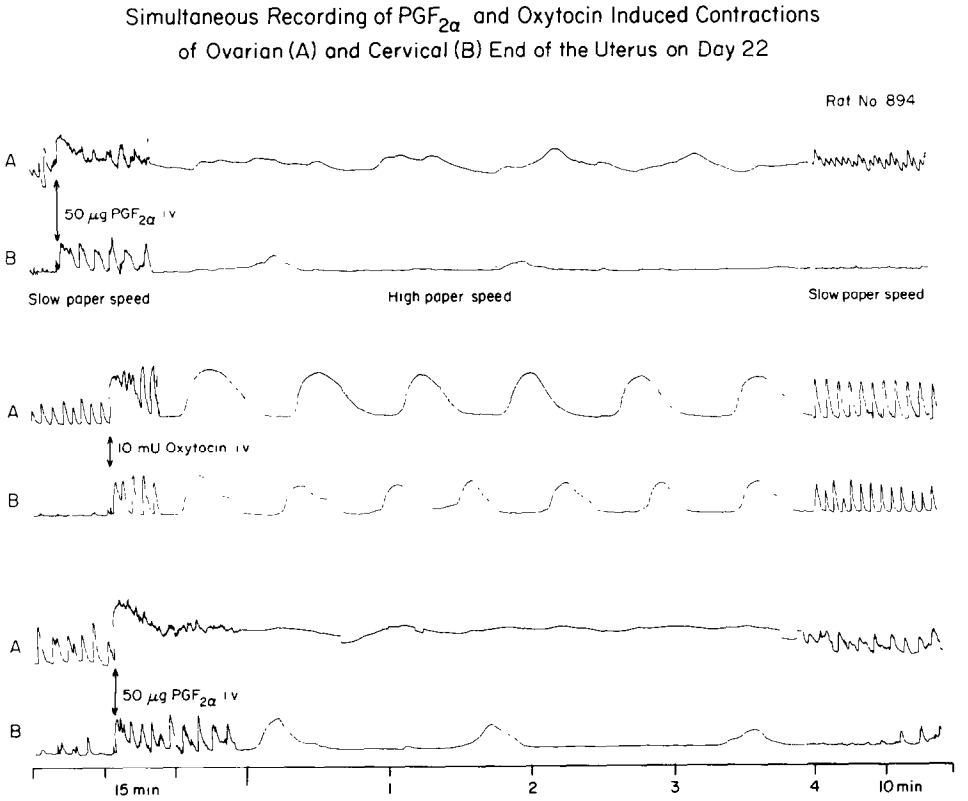

Fig. 1. Influence of oxytocin (OT) and PGF2alpha administered in equipotent doses on propagation of contractions in late pregnant rat uterus *in vivo*. Intrauterine pressure was recorded simultaneously at the ovarian end (A) and cervical end (B) of the same uterine horn. Note the asynchrony of the PGF2alpha-induced contractions and the marked synchronizing effect of oxytocin.

vivo conditions since prostaglandins are produced locally and reach the myometrial cell by diffusion from the adjacent decidua. They therefore activate only a fraction of the myometrial cells at any one time whereas oxytocin reaches the uterus via a systemic route and thus activates all receptor-bearing cells simultaneously and thus causes synchronized activity.

CONCLUSIONS

On the basis of these observations and work performed by others we propose that two types of oxytocin receptors exist, analogous to the vasopressin receptors V1 and V2. The cellular response to the occupation of oxytocin receptors in the myometrium is contraction and the response to those in the endometrium and perhaps also in the ovary is prostaglandin synthesis. Both types of receptors probably utilize C^{2+} in signal transmission. The first type acts by opening the voltage-dependent Ca^{2+} channels to increase intracellular free Ca^{2+} concentration to a range which activates the contractile machinery (Fig. 2). The second type may activate the inositol triphosphate-diglyceride pathway to increase intracellular Ca^{2+} and to activate phospholipase C which in conjunction with diacylglycerol lipase liberates arachidonic acid from diphosphatidyl inositol leading to PGE and PGF2alpha synthesis [70] (Fig. 3). Preliminary evidence for the activation of phosphoinositol turnover in human decidua has been provided [71]. According to Berridge and Irvine[72], a coupling protein analogous to the stimulatory protein Ns, which couples adenylcyclase to the occupied beta adrenergic receptor, participates in the transmission of signals by the phosphoinositol pathway. This may be the crucial element that links the occupation of oxytocin receptors in decidual cells to the activation of the arachidonic acid cascade. The resultant prostaglandins then diffuse into the adjacent myometrium and potentiate the oxytocin-induced contractions leading to progressive labor and cervical dilatation.

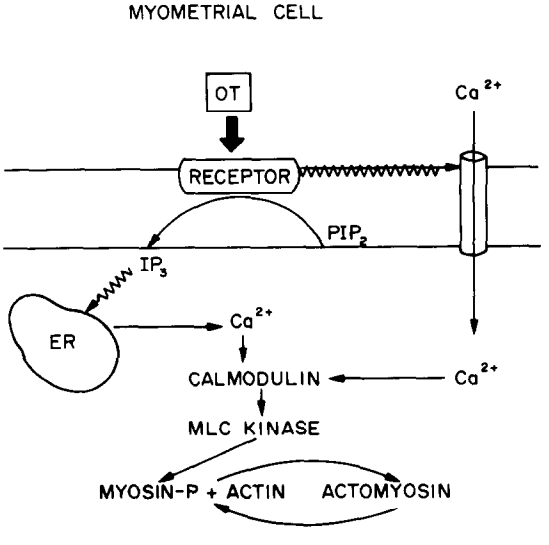

Fig. 2. Schematic representation of signal transduction in oxytocin action in myometrial cells. Oxytocin receptor occupancy activates the voltage- and receptor-dependent Ca^{2+} channels allowing extracellular Ca^{2+} to enter the cell. To a small extent oxytocin also mobilizes Ca^{2+} from intracellular stores, probably via the inositol phosphate pathway.

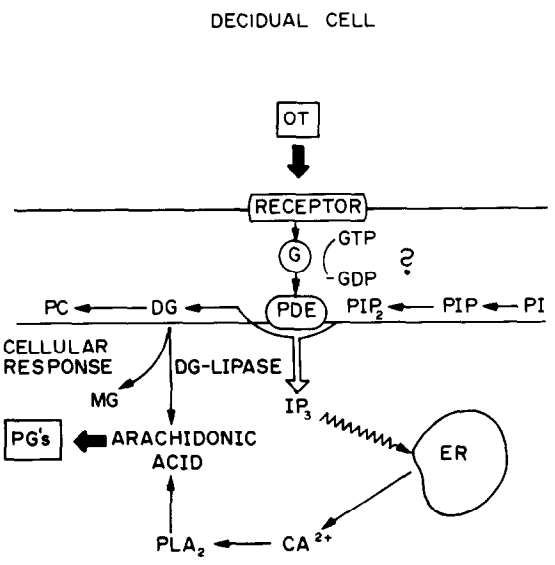

Fig. 3. Schematic representation of signal transduction in oxytocin action in decidual cells. Oxytocin receptor occupancy activates the phosphoinositol pathway which generates both inositol triphosphate and diacylglycerol as second messengers. This leads to an increase in both intracellular Ca^{2+} and free arachidonic acid which is subsequently metabolized to prostaglandins. The role of the membrane protein G in the coupling of the receptor to the phosphodiesterase that hydrolyzes the phosphatidylinositol diphosphate to form inositol triphosphate and diacylglycerol, is still hypothetical [71].

The oxytocin secreted at parturition may derive from maternal pituitary via the systemic blood, from the fetal pituitary via fetal circulation or via fetal urine and amniotic fluid [52], and/or from the placenta itself, which also contains significant amounts of oxytocin [6–8]. Ovarian oxytocin concentrations are low during pregnancy [29] and the ovary therefore contributes only a fraction of the oxytocin reaching the uterus during labor [73].

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