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Evidence for the Presence of AH 13205-Sensitive EP_2-Prostanoid Receptors in the Pregnant Baboon But Not in the Pregnant Sheep Myometrium Near Term

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OBJECTIVE: *Our purposes were to assess the effects of prostaglandin (PG) E_2 and $PGF_{2\alpha}$ on myometrial contractility in pregnant sheep and baboons in an in vitro superfusion study, and to characterize further the PGE-sensitive (EP) receptor subtype involved in the myometrial response to PGE_2 by using the selective prostanoid EP_2 agonist AH 13205.*

METHODS: *Strip preparations of uterine muscle from 15 sheep (107–145 days' gestational age) and ten baboons (158–185 days' gestation) were studied. Cumulative concentration-response curves (CRC) were constructed to oxytocin (4.2 pmol/L to 0.42 μmol/L, PGE_2 (0.1 nmol/L to 1 μmol/L), and $PGF_{2\alpha}$ (1 nmol/L to 100 μmol/L), and 50% effective concentration (EC50) values (mean and 95% confidence interval) were calculated. We also tested the hypothesis that PGE_2-induced myometrial relaxation in pregnant baboons could be mediated by EP_2-prostanoid receptors. Myometrial strips were stimulated by oxytocin (0.42 nmol/L), and CRCs to the EP_2-agonist AH 13205 (0.1 nmol/L to 10 μmol/L) were constructed.*

RESULTS: *Prostaglandin $F_{2\alpha}$ stimulated myometrial activity in a concentration-related fashion in all preparations from both sheep and baboons. The EC50 in the sheep myometrium for $PGF_{2\alpha}$ (52 nmol/L, 95% confidence interval [CI] 25–110) was significantly ($P < .05$) lower than that in baboon myometrium (183 nmol/L, 95% CI 93–355). Oxytocin stimulated myometrial activity in preparations of both sheep (EC50 = 0.29 nmol/L, 95% CI 0.11–0.71) and baboon (EC50 = 0.31 nmol/L, 95% CI 0.18–0.52). In contrast, responses to PGE_2 were species-related: PGE_2 caused concentration-related stimulation of myometrial activity in sheep tissue (EC50 = 3.2 nmol/L, 95% CI 2.0–5.0), but induced concentration-related inhibition of activity in baboon myometrium (50% inhibitory concentration [IC50] = 21 nmol/L, 95% CI 2.2–203). A concentration-related inhibitory response to AH 13205 (IC50 = 3.56 nmol/L, 95% CI 1.28–5.99) was obtained in the baboon. In contrast, AH 13205 failed to inhibit comparable myometrial strip preparations from pregnant sheep.*

CONCLUSIONS: *The present studies suggest that both sheep and baboon myometrium contain prostanoid receptors that mediate stimulation. In addition, baboon myometrium, like that from the human, contains AH 13205-sensitive EP receptors (EP_2 receptors), which mediate inhibition. The pregnant baboon may therefore represent a suitable animal model for investigations into the use of EP_2 agonists for the prevention of premature labor in humans.* (J Soc Gynecol Invest 1995;2:6–12)

KEY WORDS: Receptors, prostaglandins, myometrium, sheep, baboon, pregnancy, PGE_2, EP_2 receptors.

Prostanoids, especially prostaglandins (PGs), are involved in most aspects of uterine physiology. Prostaglandins have been implicated in the mechanism of parturition both in the human and in several animal species, including nonhuman primates and sheep.[1–3] Parturition can be delayed by the administration of PG synthase inhibitors in both the rhesus mon-

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key[4] and women.[5] Moreover, several motility-related pathophysiologic conditions such as preterm[6] or dysfunctional[7] labor are associated with abnormal release of PGs. The PGs of both the E and F series (mainly PGE_2 and $PGF_{2\alpha}$) appear to be among the major factors governing the contractility of the myometrium. Although $PGF_{2\alpha}$ is consistently excitatory on myometrial preparations from all species reported to date,[8–11] the effects of PGE_2 are less consistent. Depending on the species and experimental conditions, PGE_2 has been shown to cause both excitatory and inhibitory effects on myometrial contractility.[12–14] The stimulatory effect of $PGF_{2\alpha}$ may be mediated by specific $PGF_{2\alpha}$-sensitive (FP) receptors, which may act through a variety of different post-receptor mechanisms.[15–17] Although FP receptors are present in myometrium from the rat, hamster, and probably human, they appear to be absent in myometrium from the guinea pig and cat, and in these latter preparations, $PGF_{2\alpha}$ causes its excitatory effects through interaction with the thromboxane-sensitive (TP) or even the PGE-sensitive (EP) receptor.[16]

The cellular effects of PGE_2 are mediated predominantly by EP receptors, of which there exist several subtypes. Radioligand-binding studies have identified one or two (likely two affinity states) receptors for PGE_2 in uterine tissues (myometrium and/or endometrium) in several species, including the human.[18–23] However, little information is available on the subcellular pathway and/or the functional response involved in receptor activation. Functional studies have identified at least three E-prostanoid (EP) receptor subtypes, namely EP_1, EP_2, and EP_3 receptors, in smooth-muscle tissues including myometrium.[24,25] Thus, both EP_1 and EP_3 receptors mediate smooth-muscle cell contraction by increasing intracellular calcium levels through phospholipase C-mediated inositol phosphate catabolism and/or by a Gi protein-mediated lowering of intracellular cAMP. In contrast, it appears that EP_2 receptors cause relaxant effects in myometrial cells by a Gs protein-mediated increase in intracellular cAMP.[16,26,27] The dual actions (stimulatory and/or inhibitory) of PGE on uterine motility found in some studies can, therefore, be explained in terms of interaction with either receptor subtype: the nature of the uterine contractile response to endogenous or exogenous PGE_2 depends on which EP receptors are present and functional in the plasma membrane of myometrial cells in a given physiologic situation. The hamster is the only animal species for which EP-inhibitory receptors have been identified firmly in myometrium. Experimental evidence based on differences with the EP_2 subtype in the relative rank order of potency for selective agonists[14] has indicated that this inhibitory receptor is more likely to be of the recently identified EP_4 subtype.[28] So far, only human myometrium appears to contain EP_2 receptors.[12,13] The lack of an adequate animal model with which to complement and extend human studies precludes the development of EP_2 agonists as tocolytic agents for the prevention of premature labor in pregnant women.

The present study was performed on isolated, perfused myometrial strips obtained under halothane anesthesia from late-pregnant ewes and baboons. The objectives of the study were to evaluate the direct actions of PGE_2 and $PGF_{2\alpha}$ on myometrial contractility and to produce evidence for inhibitory EP receptors by using the selective EP_2 agonist AH 13205[28–31] on myometrial strips from both species, precontracted with oxytocin. AH 13205 is an EP_2-receptor agonist with little or no activity either at other types of EP receptor[27] or at the other types of prostanoid receptor (DP, FP, IP, and TP receptors, defined as receptors with the highest affinity for PGD_2, $PGF_{2\alpha}$, PGI_2, and TXA_2, respectively.).[29]

MATERIALS AND METHODS

Processing of Myometrial Tissue

Pieces of full-thickness uterine wall were collected at the beginning of surgical procedures under halothane general anesthesia from pregnant animals of known gestational age. In sheep, these specimens were taken midway from the uterotubal junction and the cervix in the antimesometrial border (great curvature) of the fetus-bearing uterine horn. In baboons, the myometrial tissue was taken from the ventral surface of the uterus in the fundal region or body. The exact site depended upon the location of the placenta. We studied a total of 15 Columbia × Rambouillet cross-breed ewes (Ovis aries, 50–70 kg) between 107 and 145 days of gestation with singleton or multiple pregnancies (term 148 days), and ten baboons (Papio cynocephalus, 24–30 kg) between 158 and 185 days of gestation and bearing a single fetus (term 184 days). Tissues were placed rapidly at 4°C in Krebs buffer of the following composition (mmol/L: NaCl, 118.0; $NaHCO_3$, 25.0; KCl, 5.0; KH_2PO_4, 1.0; glucose, 11.0; and $CaCl_2$, 1.3. The cyclo-oxygenase blocker indomethacin (3 μmol/L) was added to the buffer to prevent post-collection synthesis of endogenous PGs, which could interfere with the contractility of the collected tissue. Studies were approved by the Cornell University Institutional Animal Care and Use Committee.

Tissue Preparation

The endometrium was removed gently with the aid of a glass slide and dissection forceps. Myometrial tissue was then cut with a scalpel blade. Individual strips (approximately 0.4 × 1 cm) were prepared in the direction of the longitudinal muscle fibers. A long cotton thread was sutured to the upper end of each muscle strip for attachment to a force transducer (UF1, Pioden Controls Ltd., Canterbury, UK), and the lower end was anchored to the bottom of the superfusion chamber. The distance between the two sutures, measured under 1 g of tension, was found to be in the range of 9–12 mm for all the strips

used in the study. Care was taken not to allow the tissues to dry during preparation.

Muscle Superfusion System

The superfusion system used was similar to those described previously.[13,32] In each study, eight strips of myometrium were placed in individual chambers. Oxygenated (95%/5% O_2/CO_2) Krebs buffer (35–37°C), of the composition described above and containing indomethacin (3 μmol/L), was superfused onto the myometrial strips using eight channels of a 16-channel individual-cartridge peristaltic pump (CR 07618-60, Ismatec, Cole-Parmer, Chicago, IL) equipped with calibrated vinyl tubing (2.5 mm internal diameter). The system achieved a flow rate of 2.0 mL/minute. Care was taken that the nutrient buffer dripped down the cotton thread and spread over the whole strip in each chamber. A lower hole in the chamber was connected to a waste collector. Drugs were instilled into the flow of nutrient buffer using the remaining eight channels of the peristaltic pump, which were equipped with narrow-bore calibrated vinyl tubings (0.25 mm internal diameter) to produce a rate of flow for drug solutions 1/100 of that for the buffer. This dilution was taken into account when determining the final concentration of drug that actually came in contact with the superfused tissues.

Contractility Data Acquisition

After placement in the superfusion chamber, a resting tension of 1 g was applied to each myometrial strip, which was then allowed to equilibrate for 1–2 hours until a regular contractility pattern developed. Tension changes produced during the study ranged from 1–20 g, and were sampled at 32 Hz using a Data Acquisition System[33] connected to an IBM class PC computer. The computer was programmed for real-time analysis, and printers were used to output strip-chart representations of muscle activity and integrated drug-induced effects. Baseline contractility activity for each channel was defined as the average tension (g) computed for the 10-minute period immediately before administration of a drug. Drugs were administered for 12 minutes. The differences between baseline myometrial activity and the levels achieved during the final 10 minutes of the 12-minute period of drug treatment were computed on-line. Drug concentrations used covered the range from that producing no effect to that achieving a maximal activity response, as determined in previous pilot studies.

Experimental Schedule

In the first study, myometrial strips were superfused with PGE_2 at concentrations ranging from 100 pmol/L to 1 μmol/L (six sheep and four baboons), and with $PGF_{2\alpha}$ from 1 nmol/L to 100 μmol/L (nine sheep and five baboons).

In the second study, to evaluate the effects of AH 13205, the muscle strips were precontracted. This was considered necessary because in tracheal smooth muscle, PGE_2 has been shown to be stimulatory on low-tone preparations but consistently inhibitory on precontracted strips.[34] Thus, concentration-response curves (CRCs) to oxytocin were constructed cumulatively in myometrial strips from five sheep and five baboons using concentrations of 4.2 pmol/L to 0.42 μmol/L. Myometrial activity was driven by adding oxytocin up to the 50% effective concentration (EC50) into the nutrient Krebs buffer. For the study of AH 13205, the CRCs were constructed over the range of 0.1 nmol/L to 10 μmol/L of AH 13205 in muscle stimulated with 0.42 nmol/L oxytocin.

Curve Fitting

Contractility data from the different replicates (two to eight for each concentration in each animal were averaged and normalized to percent of maximal effect. A nonlinear regression curve-fitting program (GraphPad V2.0, ISI software, Philadelphia, PA) was used for fitting the replicates for each drug-concentration point for all the animals of each experimental group to a sigmoid curve, using the logistic equation:

$$E = Emax \times [D]s / EC50s + [D]s,$$

in which E = the effect of a given concentration of drug; Emax = the maximal achievable effect (top of the curve); [D] = the concentration of drug; EC50 = the concentration of drug that achieves 50% of Emax (for investigations of inhibitory effects, the term EC50 was replaced by IC50, with a similar definition); and exponent s = the slope factor. From this overall CRC fit, drug potencies were calculated for each species as the EC50 or its negative logarithm (−log EC50 or pD_2).

Statistics

Because EC50s for a given drug are not normally distributed, we used the corresponding mean pD_2 (± standard error of the mean [SEM]) values to calculate the 95% confidence interval (95% CI, calculated as $\pm t \times SEM$, using t values for the corresponding degrees of freedom) as an indication of the dispersion of the overall mean EC50 for each drug and each species. Intra-species differences (sheep versus baboon) in drug potencies, or effects of treatments (saline versus drug), were assessed where relevant using the Mann-Whitney test. Differences with $P < .05$ were considered significant.

Drugs

Prostaglandins E_2 (Dinoprostone, MW 352.5) and $F_{2\alpha}$ (Dinoprost tromethamine [THAM] salt, MW 475.6) were gifts from the Upjohn Company (Kalamazoo, MI). Stock solutions of PGE_2 (1 mmol/L) were prepared in absolute ethanol and stored at −20°C. Serial dilutions

were done in phosphate-buffered saline (NaCl, 120 mmol/L; KCl, 2.7 mmol/L; KH_2PO_4-Na_2HPO_4, 10.0 mmol/L; Sigma Chemicals, St. Louis, MO). Prostaglandin $F_{2\alpha}$ as a 5-mg/mL (11 mmol/L) THAM salt (LUTALYSE) was stored at room temperature. Oxytocin (Butler, Columbus, OH) was stored at 4°C as a saline solution (42 μmol/L). The EP_2 receptor subtype selective agonist AH 13205 (trans-2-(4-[1-hydroxyhexyl]phenyl)-5-oxocyclopentaneheptanoic acid; gift from Glaxo, Ware, Herts, UK) was stored at −20°C as a 1-mmol/L solution in absolute ethanol. Indomethacin (Sigma Chemicals) was dissolved (5 mg/mL) in absolute ethanol before being added to Krebs buffer at a final concentration of 3 μmol/L. Fresh solutions were prepared each day, left in ice until use, and discarded after each experiment.

RESULTS

Spontaneous Contractility Pattern

After equilibration, all myometrial strips studied displayed a characteristic pattern of contractility. The pattern consisted of the cyclic occurrence of contractile episodes of slightly less than 1 minute in duration, followed by relatively longer periods of quiescence. In sheep myometrium, episodes of 51.6 ± 5.0 seconds and a mean amplitude of 5.37 ± 0.34 g occurred at intervals of 143.4 ± 10.6 seconds (mean ± SEM, n = 10). The mean values calculated for each sheep were obtained from at least 20 contractile episodes per animal. In baboon myometrium, episodes lasted 33.1 ± 8.3 seconds, had a mean amplitude of 1.9 ± 0.3 g, and occurred at intervals of 144.4 ± 53.7 seconds (mean ± SEM, n = 5). The mean values calculated for each baboon were obtained from at least ten contractile episodes per animal.

Effects of PGE_2 and $PGF_{2\alpha}$ on Myometrial Contractility

Table 1 summarizes the agonist potencies of PGE_2 and $PGF_{2\alpha}$ on myometrial strips from both species. In sheep myometrium, both $PGF_{2\alpha}$ and PGE_2 caused concentration-related increases in myometrial activity (Figure 1), with EC50 values of 52 and 3.2 nmol/L, respectively. In contrast, in baboon myometrium, $PGF_{2\alpha}$ again caused concentration-related stimulant activity (EC50 = 183 nmol/L), but PGE_2 caused concentration-related inhibition (IC50 = 21 nmol/L) (Figure 1).

Effects of Oxytocin

As expected, oxytocin (4.2 pmol/L to 0.42 μmol/L) caused concentration-related increases in myometrial activity in both species (Figure 2). In sheep myometrium, the EC50 for oxytocin was 0.29 nmol/L (95% CI 0.11–0.71), and in baboon myometrium, the EC50 value was 0.31 nmol/L (95% CI 0.18–0.52) (Table 2). These values were not significantly different from each other. Oxytocin (0.42 nmol/L) consistently increased the activity of myometrial strips from both baboons and sheep by two to three times the spontaneous activity level. This effect was maintained for at least 2 hours (data not shown). Consequently, this concentration of oxytocin was chosen to drive myometrial motility, and the activity level obtained was considered as 100% baseline activity for the following study.

Table 1. Agonist Potencies of Prostaglandin E_2 and Prostaglandin $F_{2\alpha}$ in Pregnant Sheep and Baboon Myometrium in Late Gestation

	Sheep	Baboon
$PGF_{2\alpha}$	(n = 9)	(n = 5)
EC50 (nmol/L)	52	183*
95% CI	25–110	93–355
Gestation (d)	107–145	159–184
PGE_2	(n = 6)	(n = 5)
EC50 (nmol/L)	3.2	
95% CI	2.0–5.0	
IC50 (nmol/L)		21
95% CI		2.2–203
Gestation (d)	120–144	159–184

PG = prostaglandin; EC50 = concentration giving 50% stimulation of myometrial activity; CI = confidence interval; IC50 = concentration giving 50% inhibition of myometrial activity.
* Significantly different from the EC50 value in sheep ($P < .05$).

Effects of AH 13205

Both AH 13205 superfused at increasing concentrations (0.1 nmol/L to 10 μmol/L) and saline vehicle failed to modify the level of oxytocin-driven activity in sheep myometrial preparations (Figure 3A). In baboon myometrium, however, the same range of concentrations of AH 13205 caused a concentration-related inhibition of oxytocin-driven myometrial activity (IC50 = 3.56 nmol/L, 95% CI 1.28–5.99), whereas saline vehicle again produced no effect (Figure 3B, Table 2).

DISCUSSION

The present study, using an in vitro smooth muscle superfusion system, confirms the already well-documented stimulant action of $PGF_{2\alpha}$ on both pregnant sheep and baboon myometrium in late gestation. Myometrial contractile responses to $PGF_{2\alpha}$ analogues have been reported both in vivo and in vitro, e.g., in humans,[10] non-human primates,[8] sheep,[9] and rats.[11] However, our data also show a species-dependent effect of PGE_2 on myometrial contractile activity. Prostaglandin E_2 caused a clear concentration-related stimulation of motility in sheep myometrial strips, but caused a concentration-related inhibition of motility in comparable strips from the baboon myometrium.

A species-specific, concentration-related effect of the selective prostanoid EP_2 agonist, AH 13205, on oxytocin-induced contractile activity was demonstrated in myometrial muscle from the pregnant baboon. In contrast, there was no effect of AH 13205 on the motility of

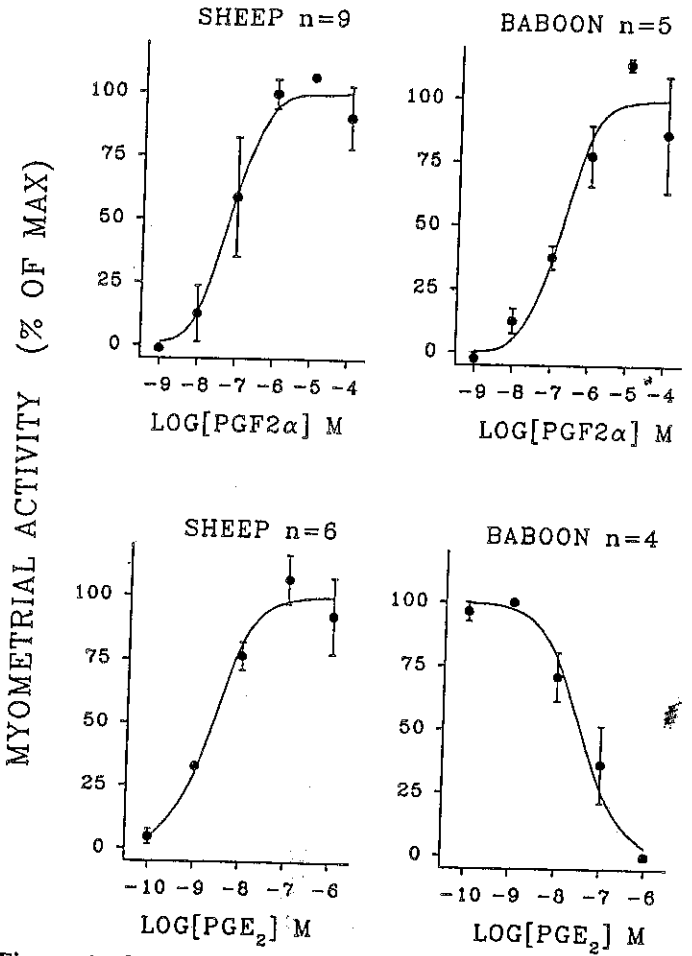

Figure 1. Cumulative CRCs for prostaglandin (PG)$F_{2\alpha}$ and PGE_2 obtained in superfusion studies with myometrial strips from sheep and baboons in late gestation. The CRCs are curves of best fit, calculated iteratively using a nonlinear regression program. Plotted values are the mean ± SEM for the *n* animals in each experimental group (*n* values for the four CRCs are different within each species because some myometrial samples were not tested with both PGs). Drug potency was calculated as the EC50 for each species (see text for details and definitions).

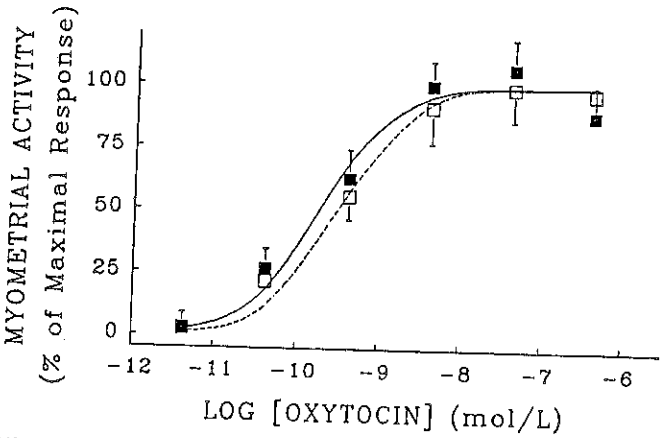

Figure 2. Concentration-response curves (mean ± SEM) to oxytocin for myometrial strips from five pregnant sheep at 122–144 days' gestation (*open squares*) and five baboons at 158–185 days' gestation (*closed squares*). Tension is represented as a percentage of maximum oxytocin response. Values from each animal were obtained from at least two replicates per data point and per animal. The plotted curves are lines of best fit obtained by nonlinear regression analysis.

comparable strips from pregnant sheep myometrium. Because AH 13205 has been shown to be essentially inactive at other potentially inhibitory prostanoid receptors, such as IP or DP receptors,[16] our findings suggest that functional EP receptors are present on the plasma membrane of myometrial cells and mediate the inhibitory effect of AH 13205 in the baboon. In contrast, EP_2 receptors are either absent or not functionally coupled in the myometrium of late-pregnant ewes.

The species-specific myometrial response to PGE_2 is interesting. Prostaglandin E_2 is thought to exert its cellular effects primarily by an action on prostanoid EP receptors, of which there are at least three subtypes: EP_1, EP_2, and EP_3. The interaction of endogenous and/or exogenous PGE_2 with these receptor subtypes initiates different intracellular regulatory cascades in myometrial smooth-muscle cells. Both EP_1 and EP_3 receptor subtypes mediate excitatory responses by increasing intracellular calcium levels and/or by lowering intracellular levels of cAMP. Conversely, EP_2 receptor activation leads to inhibitory responses, which appear to be secondary to increases in intracellular levels of cAMP.[16] Recently, however, another EP-receptor subtype, termed EP_4, has been identified in the hamster myometrium.[14] Like the EP_2 receptor, this receptor is inhibitory and appears to produce its effects through increases in intracellular cAMP, but it differs from EP_2 by different rank order of potency of relatively selective agonists.[14] These differences between species, in overall activity as well as in the nature of the inhibitory receptor subtypes (EP_2 or EP_4), clearly demonstrate the need for an experimental model that resembles as closely as possible the pregnant human myometrium.

It is likely that not all species possess all of the EP-receptor subtypes, or if they do, they are not all functionally coupled to their intracellular signaling pathways. Functional EP_1 and EP_3 receptors have been characterized pharmacologically in the myometrium of a variety of animal species, including guinea pig, rat, hamster, cat, and human.[16] Conversely, to date, experimental evidence

Table 2. Effects of Oxytocin and AH 13205 in Pregnant Sheep and Baboon Myometrium in Late Gestation

	Sheep (n = 5, 122–144 days' gestation)	Baboon (n = 5, 158–185 days' gestation)
Oxytocin		
EC50 (nmol/L)	0.29	0.31
95% CI	0.11–0.71	0.18–0.52
AH 13205		
IC50 (nmol/L)	No effect	3.56
95% CI		1.28–5.99

Abbreviations as in Table 1.

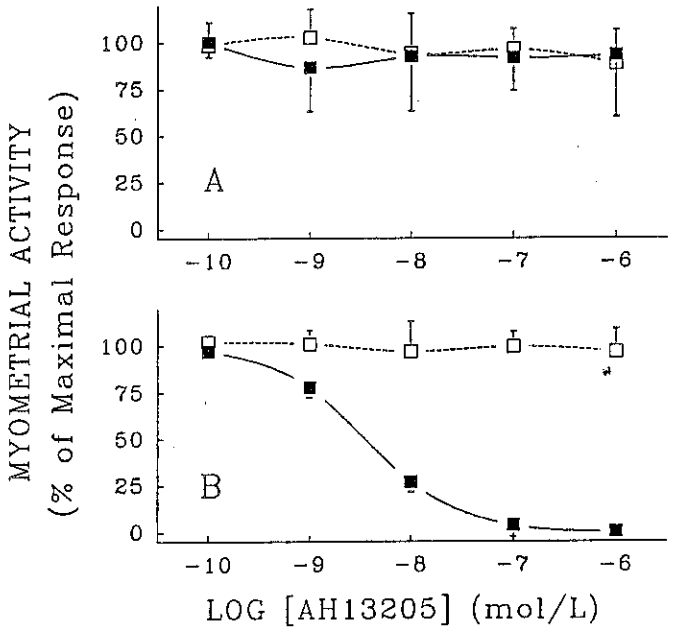

Figure 3. Effect of increasing concentrations of AH 13205 on oxytocin-driven myometrial activity from the same pregnant sheep (A) and pregnant baboon (B) as in Figure 2. Tension is represented as percentage of the activity level elicited by a continuous superfusion of oxytocin (0.42 nmol/L) maintained throughout an additional superfusion of AH 13205 (*closed squares*) or phosphate-buffered saline (*open squares*). Values are the mean ± SEM from two replicates for each data point and each animal.

for the presence of functional EP_2 receptors in the myometrium has been restricted to the human.[13] Drawing a comprehensive picture of uterine prostanoid receptors would have important implications in clinical obstetrics. Indeed, PGE_2 has been used successfully to improve the rate of cervical ripening during term labor in humans,[35] and it has been shown to soften the ovine cervix in vitro.[36] However, the lack of consistency of PGE_2 effects on uterine contractility (inhibition or activation) remains a concern for the clinician. Synthetic analogues of PGE_2 would be most likely to be effective if their stimulatory effects (cervical ripening and myometrial stimulation) and their inhibitory effects (myometrial tocolysis) could be dissociated. This could be achieved if these effects were mediated by different receptor subtypes and if selective agonists and antagonists for each receptor subtype become available. Thus, EP_1 and/or EP_3 agonists could be used to improve management of problems due to inadequate myometrial activity during parturition, whereas EP_2 agonists could be intended for clinical use as tocolytics in the treatment of premature labor. In addition, EP_2 agonists such as AH 13205 might be useful when PGE_2 is used to induce cervical dilatation, if the effects of PGE_2 on the cervix were unaffected by AH 13205, while permitting AH 13205 to inhibit any unwanted uterotonic action of PGE_2. So far, the lack of an appropriate animal model for human myometrial tissue has impeded progress in the development of EP_2-receptor selective drugs.

In conclusion, the $PGF_{2\alpha}$-induced stimulation of the myometrium of both pregnant baboons and sheep is in agreement with results obtained with a wide range of species, including the human. In view of its high potency, PGE_2-induced stimulation of sheep myometrium can be explained most likely by an interaction with stimulatory EP_1 and/or EP_3 receptors. Because $PGF_{2\alpha}$ alone caused contraction of baboon myometrium, it is tempting to speculate that FP receptors are involved. However, $PGF_{2\alpha}$ demonstrated a rather low absolute potency in this effect. Thus, further experiments with other more selective agonists and antagonists will be required to characterize definitively the receptors involved in the baboon myometrial contractile response to $PGF_{2\alpha}$. We hypothesize, however, that the stimulatory response of the myometrium to $PGF_{2\alpha}$ is mediated by TP or even EP_1 and/or EP_3 receptors, as in other tissues and species.[16] The data obtained in the second part of our study, featuring oxytocin-induced stimulation of myometrial strips from both pregnant baboons and sheep and subsequent challenge with the selective EP_2-receptor agonist AH 13205, provide pharmacologic evidence that the prostanoid receptor(s) involved in the inhibitory effect of PGE_2 in baboon myometrium is of the EP_2 subtype.

Further in vitro experiments testing other selective EP agents in parallel functional and radioligand binding studies in baboon myometrium would provide more definitive evidence as to the nature of the different EP receptors actually present in the myometrium (stimulatory and/or inhibitory), and would determine any regional or gestational-age-related changes in both non-human and human myometrium. However, the present work clearly indicates that the baboon may represent a suitable animal model for investigating the potential of EP_2 agonists in the control of myometrial hyperactivity in humans. A major advantage of this model is the ability to study activity in vivo using chronic recording of myometrial electrical activity and changes in intrauterine pressure[37] in the pregnant baboon. Thus, in vitro contractility of myometrial preparations can be equated precisely with the in vivo function of the same specimens.

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