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Anatomical differences in uterine sensitivity to prostaglandin $F_{2\alpha}$ and serotonin in non-pregnant rats

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Abstract

The ovarian steroids regulate the sensitivity of a population of uterine receptors to prostaglandin $F_{2\alpha}$, serotonin and oxytocin. However, the uterine sensitivity to prostaglandin $F_{2\alpha}$ and oxytocin does not coincide with the estrogen-induced increase in the number of receptors. Anatomical differences affect the uterine sensitivity to agonists. We investigated whether anatomical differences between ovarian and cervical uterine regions modulate the hormone-regulated sensitivity to prostaglandin $F_{2\alpha}$, serotonin and oxytocin. Non-cumulative concentration–response curves for these agonists were recorded for ovarian and cervical uterine segments from adult ovariectomized rats treated with 17β-estradiol, 17β-estradiol + progesterone, or vehicle. The ovarian segments displayed a higher maximal response (E_{max}) to prostaglandin $F_{2\alpha}$ and a lower E_{max} to serotonin than the cervical segments. Both uterine segments displayed a similar sensitivity to oxytocin. The ovariectomized controls displayed the highest E_{max} and the lowest effective concentration 50 (EC_{50}) for oxytocin and prostaglandin $F_{2\alpha}$. Anatomical differences between ovarian and cervical uterine regions modulate the hormonal regulation of uterine sensitivity to serotonin and prostaglandin $F_{2\alpha}$ in the non-pregnant rat uterus.

Keywords: Ovarin uterine segment; Cervical uterine segment; Serotonin; Prostaglandin $F_{2\alpha}$; Oxytocin; Uterine contractility

1. Introduction

The ovarian steroids, estrogens and progesterone play a central role in the regulation of uterine smooth muscle contractility. Several studies have shown the influence of estrogens and progesterone on the sensitivity to serotonin and the characteristics of the receptors for serotonin (Ichida et al., 1984; Campos-Lara et al., 1990), oxytocin (Soloff, 1975; Fuchs et al., 1983; Umscheid et al., 1998), and prostaglandin $F_{2\alpha}$ (Lintner et al., 1989). In addition, estradiol increases the synthesis of oxytocin itself, as assessed by the mRNA levels in rat uterus, whereas progesterone has no effect; a strong synergism can be observed with the two hormones (Lefebvre et al., 1994).

These studies suggest that estrogens and progesterone regulate the uterine sensitivity to agonists by means of hormone-induced changes in the population of their respective receptors. However, in some cases this relation is not clear. Some authors have found that the higher density of oxytocin binding sites in estrogen-dominated than in progesterone-dominated uteri from ovariectomized rats does not correspond with a higher contractile activity. On the contrary, they have observed that the contractile response to oxytocin was similar in estrogen-dominated and in progesterone-dominated uteri (Ruzycky and Crankshaw, 1988). Moreover, no significant variation in oxytocin-induced contractile response was observed in different phases of the menstrual cycle (Bossmar et al., 1995).

One of the factors involved in this lack of correlation might be the hormonal condition of the model used, either pregnant or non-pregnant. Nevertheless, this is not the only one, and the selection of a particular anatomical region might also be relevant. For instance, Crankshaw (1987) found that the longitudinal smooth muscle layer of the uterus is as sensitive to oxytocin on day 10 of pregnancy as it is at term, whereas the circular smooth muscle layer is

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refractory to the hormone until day 21 of pregnancy, when its sensitivity becomes similar to that of the longitudinal layer. Another type of regionalization has been observed in the pregnant rat: from day 17 coordinated regular contractions can be recorded in distal segments of the pregnant horn, while minimal or no activity is recorded in proximal segments (Gorodeski et al., 1990). In accordance with these results, we have found anatomical differences in the uterine sensitivity to serotonin and prostaglandin $F_{2\alpha}$ in cycling rats (Oropeza et al., 2000). These data suggest that the population of receptors might be heterogeneously distributed between ovarian and cervical uterine regions, and consequently each region displays a different sensitivity to agonists.

These findings prompted us to evaluate whether the anatomical region, besides the hormonal stage, is involved in the regulation of the myometrial sensitivity to oxytocin, prostaglandin $F_{2\alpha}$ and serotonin in the non-pregnant rat uterus. For this purpose, we used both ovarian and cervical uterine segments from non-pregnant ovariectomized rats treated with estradiol benzoate, estradiol benzoate + progesterone, or vehicle.

2. Materials and methods

2.1. Animals

Adult female Sprague–Dawley rats (200–250 g body weight (b.w.), bred in our laboratory, were kept under a reversed 12 h light–12 h dark schedule, with food and water available ad libitum. Only animals with at least two regular 4-day consecutive estrous cycles, determined by daily vaginal smears, were included in the study. Selected rats were ovariectomized by bilateral incision under xylocaine (20 mg/kg, i.m.) and ketamine (45 mg/kg, i.m.) anesthesia. Fifteen days after ovariectomy, rats were treated by subcutaneous injection, with (A) estradiol benzoate (40 μg/kg b.w.) 48 h prior to the experiment; (B) estradiol benzoate (40 μg/kg b. w.) 48 h + progesterone (2 mg/kg b.w.) 4 h prior to the experiment; and (C) vehicle (corn oil). Hormone doses were injected in a volume of 0.2 or 0.1 ml each in group B. The rats were killed by decapitation and the uterine horns were removed. Rings, approximately 5–7 mm long, were dissected from both the cervical and the ovarian segments of each uterine horn; thus four segments were obtained from each rat. The hospital ethics committee previously approved the protocol.

2.2. Contractile activity assays

Uterine segments were placed longitudinally in a 5-ml organ bath containing Krebs–Ringer–Bicarbonate (KRB) solution with the following composition (mM): NaCl, 120; KCl, 4.6; KH_2PO_4, 1.2; $MgSO_4$, 1.2; $CaCl_2$, 1.5; $NaHCO_3$, 20, and glucose 11. KRB solution, pH 7.4, was maintained at 37 °C and gassed continuously with a mixture of 95% O_2–5% CO_2. Each uterine segment was placed under optimum resting force of 1 g and allowed to equilibrate for 1 h before exposure to drugs; during this equilibration period, tissues were washed with fresh KRB every 10 min. The contractile responses of the segments were recorded isometrically with a tension transducer FT03 Grass connected to a polygraph Grass model 7B. To avoid the uterine synthesis of prostaglandins that may participate in the spontaneous activity and in the contractions induced by oxytocin, indomethacin (final concentration, 10 μM) was added to the KRB solutions. Non-cumulative contractile concentration–response curves for oxytocin (0.1–100.0 mIU/ml), prostaglandin $F_{2\alpha}$ (10^{-9}–10^{-4} M), or serotonin (3.2×10^{-8}–10^{-5} M) were obtained by a stepwise increase in concentration after wash out of the preceding concentration every 10 min. Each dose of the agonist remained in the tissue bath for 10 min. Each agonist was tested in a separate segment; thus each case (n) was obtained from a different rat.

2.3. Drugs

Serotonin (5-hydroxytriptamine) creatinine sulfate complex, prostaglandin $F_{2\alpha}$ tris salt, 17β-estradiol-3-benzoate (BE_2), progesterone (P_4) and indomethacin were purchased from Sigma (St. Louis, MO, USA). Oxytocin (Syntocinon) was purchased from Sandoz (Mexico, D.F.).

2.4. Analysis of data

The 50% effective concentration (EC_{50}) values were considered as the concentration of drugs that produced 50% of the individual maximal response, and were determined by using the method of Tallarida and Murray (1981). The total uterine activity (i.e. the area under the curve inscribed by the frequency and amplitude of tissue contraction) during each 10-min interval was measured with a

Table 1
Contractile responses to oxytocin of ovarian and cervical uterine segments from ovariectomized and hormone-treated rats

	Ovarian segment		Cervical segment	
	EC_{50} (mIU/ml)	E_{max} (%)	EC_{50} (mIU/ml)	E_{max} (%)
OVX + BE_2	1.61 ± 0.13[a]	105.47 ± 4.18[b]	2.14 ± 0.28[b]	112.21 ± 7.40[b]
OVX + BE_2 + P_4	1.72 ± 0.33[a]	91.85 ± 4.86[b]	1.84 ± 0.14[b]	96.11 ± 7.43[b]
OVX	0.34 ± 0.14	289.09 ± 33.96	0.42 ± 0.07	264.98 ± 17.75

Values represent means ± S.E.M. (n = 6–8).
E_{max} represents AUC as percentage of the AUC for KCl 60 mM.
BE_2 = estradiol benzoate; P_4 = progesterone.
[a] $P < 0.05$ vs. ovariectomized control.
[b] $P < 0.01$ vs. ovariectomized control.

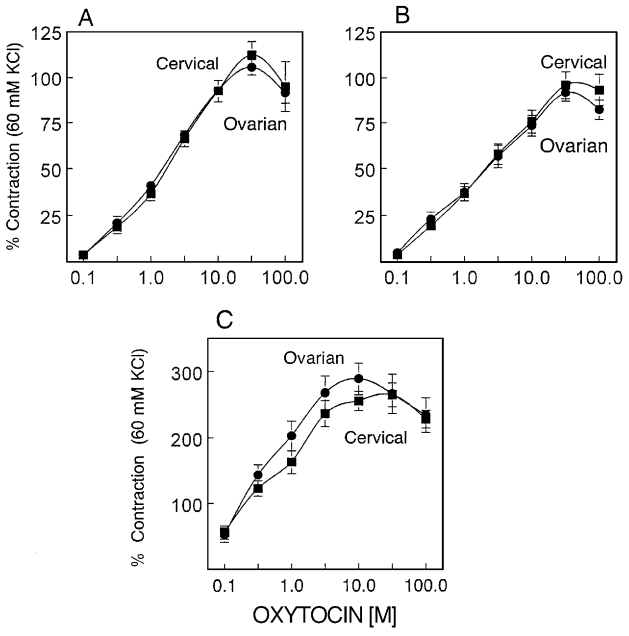

Fig. 1. Concentration–response curves for oxytocin of ovarian and cervical uterine segments from ovariectomized rats treated with: (A) estradiol benzoate; (B) estradiol benzoate + progesterone; and (C) vehicle. Each point is the mean value of six evaluations. Data represent AUC as percentage of the AUC for KCl 60 mM.

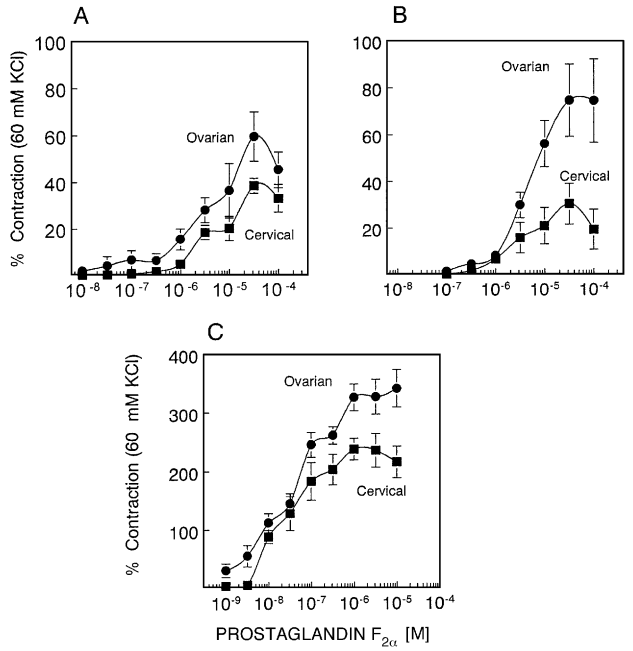

Fig. 2. Concentration–response curves for prostaglandin $F_{2\alpha}$ of ovarian and cervical uterine segments from ovariectomized rats treated with: (A) estradiol benzoate; (B) estradiol benzoate + progesterone; and (C) vehicle. Each point is the mean value of six evaluations. Data represent AUC as percentage of the AUC for KCl 60 mM.

planimeter, and the highest value obtained was considered the maximal response (E_{max}). The results are expressed as a percentage of the area under the curve of the KCl (60 mM)-induced contraction, which was considered the maximal standard response. The contractile response to high potassium was similar in the ovarian and the cervical uterine segments. For statistical comparisons between the ovarian and the cervical uterine segments, unpaired Student's *t*-test was used. Differences between the hormonal stages were evaluated with one-way analysis of variance (ANOVA), followed by Bonferroni test. $P < 0.05$ was considered statistically significant. Values reported are means ± standard error (S.E.M.)

3. Results

3.1. Oxytocin

The E_{max} and the EC_{50} for oxytocin in the ovarian uterine segments were similar to those in the cervical segments, in all groups (Table 1, Fig. 1). The ovarian and cervical segments from ovariectomized controls had higher E_{max} than those of uterine tissues obtained from ovariectomized rats treated either with estradiol benzoate or with estradiol

Table 2
Contractile responses to prostaglandin $F_{2\alpha}$ of ovarian and cervical uterine segments from ovariectomized and hormone treated-rats

	Ovarian segment		Cervical segment	
	EC_{50} ($\times 10^{-7}$ M)	E_{max} (%)	EC_{50} ($\times 10^{-7}$ M)	E_{max} (%)
OVX + BE_2	26.44 ± 4.68[a]	61.80 ± 8.87[a]	49.80 ± 9.45[a]	34.99 ± 4.79[a,b]
OVX + BE_2 + P_4	31.17 ± 10.16[a]	72.90 ± 13.88[a]	44.33 ± 9.06[a]	31.53 ± 7.26[a,b]
OVX	0.36 ± 0.14	341.05 ± 31.75	0.28 ± 0.14	237.90 ± 18.29[a]

Values represent means ± S.E.M. ($n = 6–8$).
E_{max} represent AUC as percentage of the AUC for KCl 60 mM.
BE_2 = estradiol benzoate; P_4 = progesterone.
[a] $P < 0.01$ vs. ovariectomized control.
[b] $P < 0.05$ vs. the ovarian segment.

Table 3
Contractile responses to serotonin of ovarian and cervical uterine segments from ovariectomized and hormone-treated rats

	Ovarian segment		Cervical segment	
	EC_{50} ($\times 10^{-7}$ M)	E_{max} (%)	EC_{50} ($\times 10^{-7}$ M)	E_{max} (%)
OVX + BE_2	2.80 ± 0.18	37.70 ± 6.92	3.00 ± 0.24	83.94 ± 4.50[a]
OVX + BE_2 + P_4	3.90 ± 0.65	37.17 ± 9.51	3.18 ± 0.30	69.15 ± 8.91[b]

Values represent means ± S.E.M. ($n = 6$).
E_{max} represent AUC as percentage of the AUC for KCl 60 mM.
BE_2 = estradiol benzoate; P_4 = progesterone.
[a] $P < 0.01$ vs. ovarian segment.
[b] $P < 0.05$ vs. ovarian segment.

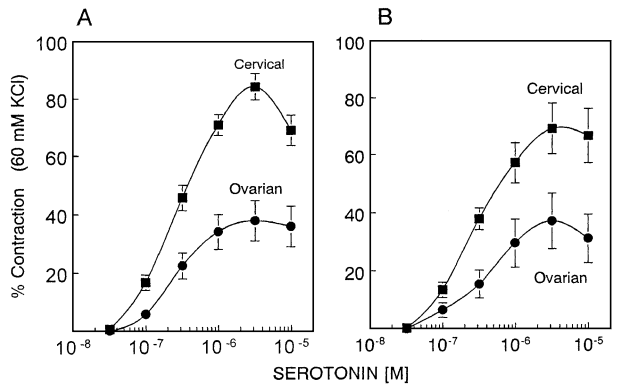

Fig. 3. Concentration–response curves for serotonin of ovarian and cervical uterine segments from ovariectomized rats treated with: (A) estradiol benzoate and (B) estradiol benzoate + progesterone. The group (C) (vehicle) was not sensitive to serotonin. Each point is the mean value of six evaluations. Data represent AUC as percentage of the AUC for KCl 60 mM.

benzoate + progesterone ($P<0.01$) (Table 1, Fig. 1). The ovarian and cervical uterine segments from ovariectomized controls had a lower EC_{50} than those of the ovarian ($P<0.05$) and cervical ($P<0.01$) uterine segments from ovariectomized rats treated either with estradiol benzoate or with estradiol benzoate + progesterone (Table 1).

3.2. Prostaglandin $F_{2\alpha}$

The E_{max} for prostaglandin $F_{2\alpha}$ in the ovarian segments was higher than that in the cervical segments ($P<0.05$) in all cases. The EC_{50} in the ovarian segments was similar to that in the cervical segments in all groups (Table 2, Fig. 2). The ovarian and cervical uterine segments from the ovariectomized controls had a higher E_{max} and a lower EC_{50} ($P<0.01$) than those from ovariectomized rats treated either with estradiol benzoate or with estradiol benzoate + progesterone (Table 2, Fig. 2).

3.3. Serotonin

Serotonin at the doses assayed did not induce a contractile response in either the ovarian, or the cervical segments from ovariectomized control rats. The E_{max} for serotonin was higher in the cervical than in the ovarian segments from ovariectomized rats treated either with estradiol benzoate ($P<0.01$) or with estradiol benzoate + progesterone ($P<0.05$) (Table 3, Fig. 3). The EC_{50} for serotonin was similar in both the ovarian and the cervical segments, and also after estradiol benzoate and estradiol benzoate + progesterone treatments (Table 3).

4. Discussion

The results of the present study indicate that the anatomical differences, besides the hormonal stage, affect the regulation of myometrial sensitivity to prostaglandin $F_{2\alpha}$ (the uterine response was higher in the ovarian than in the cervical region) and serotonin (the cervical region was more responsive than the ovarian region), but not to oxytocin, in the non-pregnant rat uterus. An unexpected finding is that ovariectomized controls, which lack the estrogenic stimulus necessary to increase the concentration of uterine receptors for oxytocin and prostaglandin $F_{2\alpha}$, displayed the highest E_{max}, and the lowest EC_{50} for these agonists.

4.1. Regionalization of contractile response to agonists

Regarding the similar response to oxytocin in both ovarian and cervical uterine regions, our data are in accord with a study of Luckas and Wray (2000), who did not find functional regionality of the human uterus in terms of the contractile response to oxytocin. Nevertheless, a more recent study reported that the contractile response and the density of receptors to oxytocin were higher in the cornua than in the cervix of the porcine myometrium (Kitazawa et al., 2001). This means that between species there are differences in the regulation of oxytocin receptor density and oxytocin-induced contractile responses.

We found that the contractile response to prostaglandin $F_{2\alpha}$ was higher in the ovarian than in the cervical segments. To our knowledge, the topographical distribution of prostaglandin $F_{2\alpha}$ receptors in the rat uterus has not been explored. In the human uterus, the corpus seems to have a higher density of prostaglandin $F_{2\alpha}$ receptors than does the cervix (Bauknecht et al., 1981). These findings support the hypothesis that the greater contractile response to prostaglandin $F_{2\alpha}$ in the ovarian segment might be related to a larger number of receptors. In the pregnant baboon uterus, prostaglandin $F_{2\alpha}$ contracts similarly the fundus myometrium and lower uterine segments (Smith et al., 1998). These controversial results with prostaglandin $F_{2\alpha}$ might be due to differences between species.

The relative involvement of prostaglandins during labor and parturition has been discussed. Recently, Engstrom et al. (2000) proposed that prostaglandin $F_{2\alpha}$ receptor stimulation may, in the absence of oxytocin receptor stimulation, exert the contractile forces needed for proper propulsion of the fetus. In the view of these and the present findings, the higher contractility in response to prostaglandin $F_{2\alpha}$ in the ovarian than in the cervical segments might act synergistically with oxytocin to provide the force necessary to expel those products located in the ovarian region.

Likewise, serotonin induces an anatomically differentiated response in the myometrium from ovariectomized rat. The cervical segment was more responsive than the ovarian segment, which displayed a minor and similar contractile response in rats treated with either estradiol benzoate or estradiol benzoate + progesterone. The present results are in accord with the finding that the contractile response of the ovarian segment to serotonin is similar during the estrous cycle, whereas the sensitivity of the cervical segment

changes according to the stages of the estrous cycle (Oropeza et al., 2000). Taken together, previous and present evidence suggests that in rat uterus the concentration of serotonin receptors might be higher in the cervical segment and lower in the ovarian segment. We are currently exploring this possibility by determining the density of serotonin receptors in both ovarian and cervical uterine segments. The greater contractile activity induced by serotonin in the cervical region suggests that serotonin might contribute to the transport of spermatozoa toward the oviduct. Further studies are needed to explore this hypothesis.

4.2. Hormonal regulation of contractile response to agonists

Concerning the influence of hormones on the oxytocin- and prostaglandin $F_{2\alpha}$-induced contractile response, we measured a greater response in tissues from ovariectomized rats than in tissues from ovariectomized and hormone-treated rats. These findings are in accord with a previous report that both the duration and dose of estradiol treatment attenuated baseline contractile activity and, in a dose-dependent manner, also reduced the sensitivity of myometrium from ovariectomized rats to oxytocin and prostaglandin $F_{2\alpha}$ (Gordan et al., 1997). In a similar manner, the increased tonus induced by oxytocin was diminished in the presence of estradiol, indicating that in term human myometrium, estradiol modulates the response to oxytocin by reducing the tonus (Fu et al., 1996). Taking together the above-mentioned and the present results, we suggest that estradiol might down-regulate the sensitivity to oxytocin in non-pregnant rat myometrium, in spite of the up-regulation of oxytocin receptors.

In a recent study, estradiol treatment of ovariectomized rats did not change either the density of prostaglandin $F_{2\alpha}$ receptors, the expression of prostaglandin $F_{2\alpha}$ receptor mRNA, or the maximal contractile activity, but did increase the EC_{50} of the prostaglandin $F_{2\alpha}$-induced contraction (Engstrom, 2001). Additionally, an increased myometrial expression of prostaglandin $F_{2\alpha}$ receptor mRNA can be observed during term and preterm labor and is temporally associated with progesterone withdrawal (Ou et al., 2000). The present findings are consistent with these findings because hormone treatment diminished the contractile response to prostaglandin $F_{2\alpha}$.

Other possible explanations for the contractile response to oxytocin and prostaglandin $F_{2\alpha}$ in the ovariectomized controls need to be investigated but are beyond the scope of the present study.

Regarding the contractile response to serotonin, we found that the ovariectomized controls did not display any contractile activity, whereas the estradiol-treated rats were responsive to serotonin. This finding coincides with previous findings on the uterine sensitivity as a late estrogenic response, since the ovariectomized controls lack and estradiol increases the number of serotonin receptors in the uterus (Campos-Lara et al., 1990; Ichida et al., 1984).

The findings of the present study show that in the non-pregnant rat uterus, the hormonal regulation of contractile activity in response to serotonin and prostaglandin $F_{2\alpha}$ might be influenced by differences between the ovarian and the cervical uterine segments. In contrast, the responsiveness to oxytocin was unaffected by the anatomical region. Further studies are required to explain the high contractility in response to oxytocin and prostaglandin $F_{2\alpha}$ seen in tissues from ovariectomized control rats.

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