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## Uterine region-dependent differences in responsiveness to prostaglandins in the non-pregnant porcine myometrium

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### Abstract

To clarify the uterine region-dependent distribution of prostanoid receptors, we compared the mechanical responses to selective prostanoid receptor agonists (FP, EP<sub>3</sub>, DP, EP<sub>2</sub>) and naturally occurring prostaglandins (PGF<sub>2α</sub>, PGE<sub>2</sub>, PGD<sub>2</sub>) in longitudinal and circular muscles isolated from three different regions (cornu, corpus and cervix) of the non-pregnant porcine uterus. Expression levels of FP receptor and cyclooxygenase (COX-1 and COX-2) in the respective regions were also examined using RT-PCR and Western blotting. The contractile responses to fluprostenol (an FP agonist) and PGF<sub>2α</sub> in both longitudinal and circular muscles were strongest in the cornu but weak in the corpus and cervix. Expression levels of mRNA and protein of FP receptor were highest in the cornu, consistent with the contractile responses. ONO-AE-248 (an EP<sub>3</sub> agonist) caused contraction of both muscle layers, but region-related difference in responsiveness was observed only in the longitudinal muscle. ONO-AE1-259 (an EP<sub>2</sub> agonist) inhibited spontaneous contraction of the myometrium, and inhibition was conspicuously stronger in the cervix. PGE<sub>2</sub> caused contraction (<100 nM, cornu > corpus = cervix) and inhibition (>300 nM, cornu = corpus ≤ cervix) of contractility depending on the concentration in both muscle layers. BW245C (a DP agonist) inhibited the spontaneous contraction, and region-dependent different responsiveness was marked in the longitudinal muscle (cervix = corpus > cornu). COX-1 but not COX-2 was detected in the non-pregnant porcine uterus. Expression level of COX-1 was different in the longitudinal muscle (cornu > corpus = cervix) but the same in the circular muscle. SC-560 inhibited the spontaneous contraction of longitudinal muscles in all regions. The results of the present study indicate that there are region-related heterogeneous distributions of contractile (FP

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and EP<sub>3</sub>, cornu > cervix) and relaxant (EP<sub>2</sub> and DP, cervix > cornu) prostanoid receptors and COX-1 in the porcine uterus. The results also suggest involvement of endogenous PGs in the regulation of spontaneous uterine contractility. Region-related differences in COX-1 and prostanoid receptors might be necessary to produce a gradient of uterine motility decreasing from the cornu to the cervix that manages movement of luminal contents.

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*Keywords:* Porcine uterus; Cornu; Corpus; Cervix; Prostaglandins; Prostanoid receptors; Cyclooxygenase

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## 1. Introduction

Prostaglandins (PGs) are produced by cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2) and specific PGs synthases from arachidonic acid, and they play important roles in reproductive functions (luteolysis, myometrium contraction, fertilization, implantation and maintenance of pregnancy), inflammation, generation of heat, modification of pain, induction of sleep and modulation of visceral smooth muscle tonus. Five endogenous ligands (PGF<sub>2α</sub>, PGE<sub>2</sub>, PGD<sub>2</sub>, PGI<sub>2</sub> and thromboxane A<sub>2</sub>) and eight prostanoid receptors (FP, EP<sub>1</sub>, EP<sub>2</sub>, EP<sub>3</sub>, EP<sub>4</sub>, DP, IP and TP) make it possible for PGs to achieve various physiological functions [1–6]. With regard to regulation of myometrial contractility by PGs, many functional and biochemical studies have demonstrated heterogeneous populations of prostanoid receptors in human, sheep, hamster, guinea-pig, rat, cat and bovine uteri [7–10] and have also indicated a notable species difference in prostanoid receptors in the uterus.

The porcine uterus is a bipartite uterus and has a relatively long cornu and short corpus and cervix, similar to rat and mouse uteri. These anatomical characteristics of the porcine uterus prompted us to determine whether physiological functions of uterine regions are different. Previous studies using cornu, corpus and cervix myometrial strips indicated uterine region-dependent differences in autonomic innervation and changes of spontaneous contractility and responsiveness to bioactive agents (acetylcholine, epinephrine, oxytocin and 5-hydroxytryptamine). Oxytocin caused contraction of uterine longitudinal muscles, and the cornu was more sensitive than were the corpus and cervix due to the heterogeneous distribution of oxytocin receptors. On the other hand, region-related differences in the responsiveness and density of receptors were not observed in circular muscles [11]. The contractile intensity to norepinephrine and acetylcholine was most potent in the cornu, slightly weaker in the corpus and weakest in the cervix among the longitudinal muscles. However, regional differences in responsiveness were not conspicuous in the circular muscle [12]. Isoprenaline inhibited the spontaneous contractility of uterine smooth muscle through activation of β<sub>2</sub>-adrenoceptor, and inhibition by isoprenaline was greater in the cervix than in the cornu and corpus in either longitudinal or circular smooth muscles [13]. Taken together these region-dependent differences in responsiveness to contractile and relaxant agents, myometrial contractility of the cornu might be higher than that of corpus and cervix and that different contractility depending on the region might produce a gradient of intraluminal pressure decreasing toward the cervix. However, to confirm this hypothesis, it is necessary to examine the regional differences in other uterotrophic agents that have potent actions in the porcine uterus.

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