Agonist and antagonist specificities of decidual prostaglandin-releasing oxytocin receptors and myometrial uterotonic oxytocin receptors in pregnant rats

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This paper describes further pharmacological characterization of the decidual prostaglandin-releasing oxytocin receptors and the myometrial uterotonic oxytocin receptors in the uterus of the pregnant rat. The effects of oxytocin, arginine-vasopressin and their related agonists and antagonists on the release of PGF₂α were studied in vitro on isolated uteri from rats on day 19–20 of pregnancy that had been incubated in Krebs buffer, pH 7.4, at 37°C. The concentration of PGF₂α in the media was measured using specific radioimmunoassays. It was found that the decidual and myometrial oxytocin receptors exhibit different ligand specificities. Of the agonists tested, oxytocin and arginine-vasopressin stimulated PGF₂α release in a dose-dependent manner. Arginine-vasopressin has only 3% of the uterotropic potency of oxytocin, but was found to have 16% of its PGF₂α-releasing activity. [4-Threonine, 7-glycine]oxytocin, a highly potent and selective uterotonic oxytocin analogue, had no detectable prostaglandin-releasing activity at a dosage 30 times higher than oxytocin. However, 1-deamino-[8-D-arginine]vasopressin, a highly potent and selective antidiuretic arginine-vasopressin analogue, which has only 10% of the uterotonic activity of arginine-vasopressin, was as potent as arginine-vasopressin in prostaglandin-releasing activity. Of the oxytocin antagonists tested, it was confirmed that [1-penicillamine, 2-O-methyl-tyrosine, 4-threonine]ornithine-vasotocin and its close congener [1-penicillamine, 2-p-methyl-phenylalanine, 4-threonine]ornithine-vasotocin are partial oxytocin antagonists and that 9-desglycinamide-[1-(β-mercaptop-β-cyclopentamethylene-propionic acid)2-O-methyl-tyrosine, 4-threonine]ornithine-vasotocin, [1-(β-mercaptop-β-cyclopentamethylene-propionic acid)2-O-methyl-tyrosine, 4-threonine]ornithine-vasotocin and 1-deamino-penicillamine [2-O-methyl-tyrosine]ornithine-vasotocin are full oxytocin antagonists. The two partial oxytocin antagonists blocked the uterotropic action of oxytocin but had agonistic activity on decidual receptors, stimulating release of PGF₂α. The full oxytocin antagonists blocked both the uterotropic and PGF₂α-releasing actions of oxytocin. Thus, the myometrial and decidual oxytocin receptors have different ligand specificities for agonists and antagonists. We propose that the two uterine oxytocin receptor subtypes be designated as OT₁a for the myometrial uterotonic receptors and OT₁b for the endometrial or decidual prostaglandin-releasing receptors.

Introduction

The mechanism that triggers the onset of labour is not known. The onset of parturition is preceded by a marked increase in the concentrations of oxytocin receptors (Alexandrova and Soloff, 1980; Soloff, 1985) and the formation of gap junctions (Garfield et al., 1980; Verhoeff and Garfield, 1986) in the myometrium. The development of these two biomolecular events may have an important role in the initiation of labour. Oxytocin has a dual action in the uterus: a uterotropic action on myometrial cells and a prostaglandin-releasing action on endometrial and decidual cells (Chan, 1980; Fuchs et al., 1982). We have shown that oxytocin receptors and gap junctions in the pregnant rat are stimulated by prostaglandin F₂α (PGF₂α), while inhibiting prostaglandin synthesis suppresses their formation and delays the onset of labour (Chan et al., 1991; Chan and Chen, 1992). Others have demonstrated that uterine tissues express the oxytocin gene during pregnancy, and that the rate of expression increases markedly near term (Lefebvre et al., 1992, 1993; Chibbar et al., 1993). These findings suggest that a paracrine or autocrine oxytocin system is involved in initiating

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labour. We postulate that oxytocin may regulate its own receptor formation and gap junction development in the myometrium via its PGF₂α-releasing action in the endometrium and decidua.

Preliminary findings showed that myometrial and decidual oxytocin receptors in the uterus of pregnant rats could be differentiated by oxytocin antagonists into subtypes (Chan et al., 1993). Presently available oxytocin antagonists may block only the uterotropic action or may block both the uterotropic and PGF₂α-releasing actions of oxytocin. Delineating the two oxytocin receptor subtypes and their ligand specificities is important both for the fundamental study of the action of oxytocin and to the clinical management of preterm labour. Characterizing the two uterine oxytocin receptor subtypes could lead to the development of myometrial-selective and endometrial- or decidual-selective oxytocin antagonists. Oxytocin antagonists selective for different receptor subtypes would provide powerful probes to investigate the role of oxytocin in the initiation of labour, and potential tocolytic agents for the treatment of preterm labour.

In this paper, we report further studies on the characterizations of the myometrial uterotropic oxytocin receptors and the decidual prostaglandin-releasing oxytocin receptors in pregnant rats. We present data showing that the two oxytocin receptor subtypes can be differentiated not only by appropriate oxytocin antagonists but also by their affinity and specificities for agonists.

**Materials and Methods**

**Materials**

The following oxytocin and vasopressin agonists and antagonists were used (with the exceptions noted below, these were synthesized in the laboratory by M. Manning): 1-deamino-[8-α-arginine]vasopressin (dDAVP) (Zaoral et al., 1967; Manning et al., 1976); [4-threonine, 7-glycine]oxytocin ([Thr⁴, Gly⁷]OT) (Lowbridge et al., 1977); 1-deamino-penicillamine [2-O-methyl-tyrosine]ornithine-vasotocin (dP[Tyr(Me)]⁵[Thr⁴]OTV) (Sawyer et al., 1980); 1-β-mercaptop-β-cyclopentamethylenepropionic acid) 2-O-methyl-tyrosine, 4-threoninejornithine-vasotocin ([d(CH₃)₂[Tyr(Me)², Thr⁴]OTV and 9-desglycinamide-[1-β-mercaptop-β-cyclopentamethylenepropionic acid] 2-O-methyl-tyrosine, 4-threoninejornithine-vasotocin (dGly-NH₂, d(CH₃)₂[Tyr(Me)², Thr⁴]OTV) (Manning et al., 1989). [1-Penicillamine, 2-O-methyl-tyrosine, 4-threoninejornithine-vasotocin ([P[Tyr(Me)², Thr⁴]OTV and [1-penicillamine, 2-p-methyl-phenylalanine, 4-threoninejornithine-vasotocin ([P[Ph(Me)², Thr⁴]OTV] (Chan et al., 1965, 1987) were synthesized in V. J. Hruby's laboratory (University of Arizona). Oxytocin and arginine-vasopressin were purchased from Peninsula Laboratories (Belmont, CA). Multilabelled [³¹]HPGF₂α was purchased from DuPont NEN (Boston, MA) and prostaglandin standards and anti-prostaglandin sera from PerSeptive Diagnostics (Cambridge, MA).

**Animals**

Pregnant Wistar rats, 60–70 days old, were purchased from Hilltop Laboratory Animals (Scottsdale, PA). Rats were mated in the morning and were examined in the afternoon for the presence of vaginal plugs (presence of plug indicated day 1 of pregnancy). Those found with plugs were identified, separated, and delivered to us on day 13 of pregnancy. The rats were housed individually in shoebox cages in our central animal care facility under a controlled photoperiod and air-conditioning. Water and food were freely available. The use of animals in this protocol was approved by the Institutional Animal Care and Use Committee.

**Experimental protocol**

The effects of oxytocin agonists and antagonists on uterine PGF₂α release in vitro were determined on isolated uteri from rats on day 19–20 of pregnancy. Rats were killed by cervical dislocation and the uterine horns quickly removed and placed in ice-cold Krebs–bicarbonate buffer at pH 7.4. The uterine horns were cut open and fetal tissues removed. Each uterine horn was divided longitudinally in half over the placental attachment sites, forming a matched pair. Thus, four matched tissues were obtained from each rat. Each uterine tissue was rinsed clean in buffer at 37°C, and was hung in an incubation chamber under a tension of 2 g. The tissues were incubated in 20 ml Krebs buffer that was aerated continuously with 95% O₂ and 5% CO₂ at 37°C.

After 20 min, the experimental incubation period was started. The incubation medium was withdrawn and replaced at 30 min intervals. After two control intervals (each of 30 min), an oxytocin agonist or an oxytocin antagonist was added to the incubation medium. The incubation continued for a further two or three 30 min periods. In each incubation experiment, one matched tissue was used as a control and was incubated only in the Krebs buffer. Three concentrations of each test peptide were studied. Only one test peptide and one concentration were tested in a given tissue preparation. Thus, from one rat, the four matched tissues were allocated to a control and three concentrations of a test peptide. In experiments in which the effects of oxytocin antagonists on the PGF₂α-releasing activity of oxytocin were determined, the antagonist was introduced 5 min before oxytocin. At the conclusion of the incubation experiment, the wet masses of the uterine tissues were measured.

PGF₂α in the control and treated incubates was extracted and determined by radioimmunoassays as described below. The rate of PGF₂α release was expressed in ng g⁻¹ tissue min⁻¹. The release rate during the second control (pretreatment) period for each tissue was taken as the basal release rate for that tissue preparation (generally between 0.20 and 0.35 ng g⁻¹ min⁻¹) and was designated the value of 100%. PGF₂α release rates in all subsequent samples were expressed as a percentage of their respective basal rates. The PGF₂α release rate of the second post-treatment incubation sample was used as the measure of response. The PGF₂α release rate of the control tissue for the corresponding period was used as the baseline stability reference. Preliminary studies showed that this experimental protocol yielded reproducible linear dose–response curves to oxytocin (Chan et al., 1993). Only the release of PGF₂α was measured, since our previous experiments have shown that other prostanoids are not significantly released by oxytocin (Chan, 1987; Chan et al., 1993).
Details of the extraction and radioimmunoassay procedures were described by Chan (1987). PGF$_{2\alpha}$ concentrations were determined in each sample and in duplicate. The anti-PGF$_{2\alpha}$ antibody used was highly specific, with no significant cross-reactions (\(<0.5\%\)) with other prostaglandins present in the uterus. The sensitivity of the radioimmunoassay was 15 pg per assay tube. The intra-assay coefficient of variation was \(<10\%\) and the interassay coefficient of variation was \(<15\%\).

In vitro oxytocin and anti-oxytocin assays

In vitro oxytocin assays were performed on isolated uteri from Wistar rats that had been pretreated the afternoon before with 50 \(\mu\)g diethylstilboestrol in oil per rat injected s.c. Mg$^{2+}$-free van Dyke–Hasting solution (Munsick, 1960) was used as the bathing medium. Agonistic potencies were determined against the USP standard using the four-point bioassay design (Holton, 1948). Agonistic potencies of the oxytocin antagonists were measured against oxytocin and expressed as $pA_2$ values (Schild, 1947).

Statistical analyses

All data were expressed as sample means $\pm$ SEM and analysed by analysis of variance. Significant differences between sample means were analysed by paired Student’s $t$ test at the $P = 0.05$ level.

Results

Effects of oxytocin/vasopressin agonists on PGF$_{2\alpha}$ release in vitro in the uteri of pregnant rats

The PGF$_{2\alpha}$-releasing activity of the four agonists (oxytocin and its uterotonic-selective analogue [Thr$^4$, Gly$^7$]OT; and arginine-vasopressin and its antidiuretic-selective analogue dDAVP) were determined in vitro in the rat uterus on day 19–20 of pregnancy.

Oxytocin, arginine-vasopressin and dDAVP stimulated PGF$_{2\alpha}$ release in a dose-dependent manner (Fig. 1). The dose range for oxytocin, 1–10 ng ml$^{-1}$, represents 0.5–5.0 mU
oxytocin activity ml⁻¹, which is in the low–moderate dose range in rat oxytocic assays in vitro. Unexpectedly, the highly potent and selective uterotonic analogue [Thr⁴, Gly⁷]OT had no PGF₂α-releasing activity at concentrations up to 30 ng ml⁻¹. In tests for antagonism, [Thr⁴, Gly⁷]OT had no inhibitory effect on the PGF₂α-releasing activity of oxytocin at doses of up to 300 ng ml⁻¹ (Fig. 2).

There was no apparent correlation between the uterotonic and the PGF₂α-releasing activities of the peptides (Table 1).

**Effects of oxytocin antagonists on PGF₂α release in vitro**

The five potent oxytocin antagonists (anti-oxytocin) were examined for their effects on PGF₂α release and their antagonism of the PGF₂α-releasing activity of oxytocin in vitro in rat uteri on day 19–20 of pregnancy. The anti-oxytocin potencies of these five oxytocin antagonists range from pA₂ values of 7.30 to 7.95. The concentrations of the oxytocin antagonists used in the experiments (30–750 ng ml⁻¹) cover the half-maximal to maximal anti-uterotonic doses of these antagonists in the pA₂ bioassay. They were effective inhibitory doses of the uterotonic response to the dose of oxytocin (2–4 ng ml⁻¹) used to stimulate PGF₂α release in the pregnant rat uterus.

In confirmation of preliminary studies (Chan et al., 1993), P[Thr(Me)², Thr⁴]OVT was found to be a partial oxytocin antagonist and desGly-NH₂, d(CH₂)₆[Tyr(Me)², Thr⁴]OVT a full oxytocin antagonist. P[Tyr(Me)², Thr⁴]OVT, a close congener of P[Thr(Me)², Thr⁴]OVT, also acts as a partial oxytocin antagonist. It blocked the uterotonic response to oxytocin but stimulated PGF₂α release (Table 2). The PGF₂α-releasing dose–response curves of these two partial oxytocin antagonists are shown (Fig. 1), together with the agonist peptides tested.

dP[Tyr(Me)²]OVT and d(CH₂)₆[Tyr(Me)², Thr⁴]OVT are full oxytocin antagonists. They, like desGly-NH₂, and d(CH₂)₆[Tyr(Me)², Thr⁴]OVT, blocked both the uterotonic and the PGF₂α-releasing actions of oxytocin. The inhibition of oxytocin-induced PGF₂α release in vitro by the three full oxytocin antagonists is dose dependent, and desGly-NH₂, and d(CH₂)₆[Tyr(Me)², Thr⁴]OVT was the most potent (Fig. 3).

**Discussion**

In one of our early studies, we found that treating pregnant rats during the last 3 days of gestation with P[Thr(Me)², Thr⁴]OVT, a long-acting oxytocin antagonist, significantly prolonged the duration of parturition, but did not delay the onset of labour or suppress oxytocin receptor and gap junction formation (Chan et al., 1991; Chan and Chen, 1992). Subsequently, we determined that P[Thr(Me)², Thr⁴]OVT was a partial oxytocin antagonist, which blocked the uterotonic action of oxytocin but had agonistic action on decidual receptors stimulating PGF₂α release (Chan et al., 1993). This could account for the failure of this antagonist to suppress oxytocin receptor formation and delay the onset of labour. The study reported here provided further evidence that the myometrial and decidual oxytocin receptors represent two subtypes.

The myometrial and decidual oxytocin receptors each had different ligand specificities for agonists and antagonists. To study the effects of agonists, we compared the uterotonic and PGF₂α-releasing potencies of oxytocin and [Thr⁴, Gly⁷]OT, a highly potent and selective uterotonic oxytocin analogue, and of arginine-vasopressin and dDAVP, a highly potent and

**Table 1. Comparison of uterotonic and prostaglandin-releasing activities of oxytocin agonists in rats**

<table>
<thead>
<tr>
<th>Peptides</th>
<th>Oxytocic potency (ng ml⁻¹)</th>
<th>Relative potency</th>
<th>Prostaglandin-releasing potency (ng ml⁻¹)</th>
<th>ED₅₀ (ng ml⁻¹)</th>
<th>Relative potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxytocin</td>
<td>520</td>
<td>1.00</td>
<td>1.4</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>[Thr⁴, Gly⁷]OT</td>
<td>857</td>
<td>1.76</td>
<td>30 (no effect)</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Arginine-vasopressin</td>
<td>14</td>
<td>0.03</td>
<td>9</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>dDAVP</td>
<td>1.5</td>
<td>0.003</td>
<td>10</td>
<td>0.14</td>
<td></td>
</tr>
</tbody>
</table>

*aRat oxytocin activity in vitro in USP units assayed in previous studies (Manning et al., 1976; Lowbridge et al., 1977). bConcentrations that increased the release of prostaglandins by 1.5 times the basal rate in isolated rat uteri on day 19–20 of pregnancy incubated in Krebs buffer at 37°C. cAssayed in 0.5 mmol Mg²⁺ 1⁻¹. dDAVP: 1-deamino-[8-o-arginine] vasopressin; [Thr⁴, Gly⁷]OT: [4-threonine, 7-glycinel]oxytocin.
Table 2. Comparison of effects of oxytocin antagonists on prostaglandin release in vitro from rat uteri on day 19–20 of pregnancy

<table>
<thead>
<tr>
<th>Oxytocin antagonists</th>
<th>Anti-uterotonic potency, pA₂</th>
<th>Effects on prostaglandin release</th>
</tr>
</thead>
<tbody>
<tr>
<td>P[Phe(Me)₂, Thr³]OVT</td>
<td>7.30</td>
<td>Stimulate, No effect</td>
</tr>
<tr>
<td>P[Tyr(Me)₂, Thr³]OVT</td>
<td>7.30</td>
<td>Stimulate, No effect</td>
</tr>
<tr>
<td>desGly-NH₂, d(CH₂)₅[Tyr(Me)₂, Thr³]OVT</td>
<td>7.95</td>
<td>No effect, Decrease</td>
</tr>
<tr>
<td>d(CH₂)₅[Tyr(Me)₂, Thr³]OVT</td>
<td>7.84</td>
<td>No effect, Decrease</td>
</tr>
<tr>
<td>d[P(Tyr(Me)₂)OVT</td>
<td>7.70</td>
<td>No effect, Decrease</td>
</tr>
</tbody>
</table>

⁺pA₂ Values represent the negative logarithm to the base 10 of the average molar concentration of an antagonist that will reduce the biological response to 2x units of agonist to equal the response given by x units of agonist in the absence of antagonist. In vitro assays on nonpregnant rat uteri.

Studied in the dose range 30–750 ng ml⁻¹.

Studied in the dose range 150–750 ng ml⁻¹.

Spontaneous⁵

Oxytocin-induced⁵

selective antidiuretic vasopressin (V₂ receptor) analogue in vitro. The rank orders of their relative uterotropic potencies and their PGF₂α-releasing potentials were found to be markedly different. Arginine-vasopressin possesses only a fraction (3%) of the uterotropic activity of oxytocin but was found to have 16% of the PGF₂α-releasing activity of oxytocin. (Thr⁴, Gly³)OT, the highly selective uterotropic oxytocin agonist with negligible vasopressor (V₁₄ receptor) or antidiuretic (V₂ receptor) activities and nearly two times more potency than oxytocin in uterotropic activity, when assayed in 0.5 mmol Mg²⁺ l⁻¹ (Lowbridge et al., 1977), had no detectable PGF₂α-releasing activity at a dosage 30 times higher than that of oxytocin. dDAVP is a highly potent and selective V₂ agonist (Zaral et al., 1967; Manning et al., 1976). It has an antidiuretic activity of 1200 U mg⁻¹ versus 320 U mg⁻¹ for arginine-vasopressin, but a uterotropic activity of only 10% of that of arginine–vasopressin and 0.3% of that of oxytocin (Manning et al., 1976). Its PGF₂α-releasing activity was found to be equal to that of arginine–vasopressin. The effects of the oxytocin antagonists P[Phe(Me)₂, Thr³]OVT and its close congener P[Tyr(Me)₂, Thr³]OVT (Chan et al., 1986, 1987), and of desGly-NH₂, d(CH₂)₅[Tyr(Me)₂, Thr³]OVT and its nontruncated structure d(CH₂)₅[Tyr(Me)₂, Thr³]OVT (Manning et al., 1989), and d[P(Tyr(Me)₂)OVT (Sawyer et al., 1980), were also compared. We confirmed our preliminary findings (Chan et al., 1993) that P[Phe(Me)₂, Thr³]OVT is a partial oxytocin antagonist and desGly-NH₂, d(CH₂)₅[Tyr(Me)₂, Thr³]OVT is a full oxytocin antagonist. P[Tyr(Me)₂, Thr³]OVT, like its Phe(Me)²
congener, was also found to be a partial oxytocin antagonist, both of these partial antagonists blocked the uterotropic action of oxytocin but stimulated PGF$_{2\alpha}$ release in the isolated pregnant rat uterus. However, their PGF$_{2\alpha}$-releasing potencies were 2–3 orders of magnitude weaker than oxytocin.

The peptides d(CH$_2$)$_3$Tyr(Me)$_2$, Thr$_4$OVT and dP[Tyr-(Me)$_2$OVT, like the truncated desGly-NH$_2$, d(CH$_2$)$_3$Tyr(Me)$_2$, Thr$_4$OVT, were found to be full oxytocin antagonists, which blocked both the uterotropic and prostaglandin-releasing actions of oxytocin. However, all three oxytocin antagonists were much more potent in antagonizing the uterotropic action than the PGF$_{2\alpha}$-releasing action of oxytocin. The concentrations of the antagonists used in the anti-prostaglandin-release assays (30–750 ng ml$^{-1}$) were at least a thousand times higher than those used in the pA$_2$ anti-uterotropic assays. The dose range used in the anti-prostaglandin-release assays produced maximal inhibitions of the oxytocin-induced contractions in the isolated pregnant uterus. The high doses required to block the oxytocin-induced PGF$_{2\alpha}$ release indicate that these oxytocin antagonists are poor ligands for the decidual PGF$_{2\alpha}$-releasing oxytocin receptors.

The striking differential effects between the different oxytocin antagonists on uterotropic inhibition and inhibition of PGF$_{2\alpha}$ release and the lack of PGF$_{2\alpha}$-releasing activity of the highly potent and selective oxytocin agonist [Thr$^4$, Gly$^8$]OT strongly support our postulate that the myometrial uterotonic oxytocin receptors and the endometrial/decidual prostaglandin-releasing oxytocin receptors represent two distinct subtypes. We propose, as suggested by Chan et al. (1993), that the myometrial uterotonic oxytocin receptors be designated as the OT$_{1\alpha}$ subtype and the endometrial/decidual PGF$_{2\alpha}$-releasing oxytocin receptors as the OT$_{1\beta}$ subtype. Although the number of agonists and antagonists investigated in this study was too small to allow a characterization of the ligand specificities of the two receptor subtypes, the findings do appear to suggest that deleting the amino-terminal amino group may be a requirement for inhibiting prostaglandin release. It also appears that a structure selective for V$_2$ receptors may enhance binding to decidual oxytocin receptors, as suggested by the relative PGF$_{2\alpha}$-releasing activity of arginine-vasopressin and dDAVP to their respective uterotropic activities. Further analysis of structure–activity relationships could lead to the discovery of decidual-selective and myometrial-selective oxytocin agonists and antagonists.

Premature birth is a major medical, societal and economic problem. Premature labour affects nearly 10% of pregnancies, and premature birth is the leading cause of neonatal mortality and morbidity in developed countries (Vital Statistics of US, 1982; Main, 1988). Safe and effective therapeutic intervention of preterm labour has yet to be developed. The mechanism that triggers the onset of labour is poorly understood. The marked increases in myometrial oxytocin receptor concentrations and gap junction densities at term (Soloff, 1985; Verhoeof and Garfield, 1986; Chan et al., 1991; Chan and Chen, 1992) and the recent new findings that the pregnant uterus is a major site of oxytocin synthesis at term (Lefebvre et al., 1992, 1993; Chibbar et al., 1993) suggest that a paracrine or autocrine oxytocin system may play an important role in the initiation of labour. The identification of the two oxytocin receptor subtypes in the uterus with different ligand specificities has important implications both for our understanding of the mechanism of initiation of labour and for the clinical application of oxytocin antagonists in the treatment and prevention of preterm labour.

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