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Oxytocin and vasopressin constrict rat isolated uterine resistance arteries by activating vasopressin V_{1A} receptors

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Abstract

Both oxytocin and vasopressin cause potent and long-lasting vasoconstriction of uterine arteries from several species, including humans, and the resulting tissue ischemia is thought to be involved in the pathogenesis of primary dysmenorrhea. We have studied the effects of oxytocin and vasopressin in isolated resistance arteries (diameter, 90–120 μm) from non-pregnant rat uteri using two potent and selective receptor antagonists, SR 49059, a selective vasopressin V_{1A} antagonist, and atosiban, a selective oxytocin antagonist. Uterine arteries with intact endothelium were mounted in a microvessel chamber, and pressurized to 75 mm Hg to allow the development of myogenic tone. Both vasopressin and oxytocin elicited a concentration-dependent vasoconstriction with a similar maximum effect (i.e., total vessel occlusion). The EC_{50} was 0.44 ± 0.02 and 25 ± 3.1 nM for vasopressin and oxytocin, respectively. Thus, vasopressin was 57-fold more potent than oxytocin. Schild analysis indicated that SR 49059 yielded a similar pA_2 value against vasopressin-induced ($pA_2 = 8.96 \pm 0.60$) or oxytocin-induced ($pA_2 = 9.06 \pm 0.23$) contractions, suggesting that both agonists activated the vasopressin V_{1A} receptor. In addition, atosiban (10^{-7} M), a selective antagonist of the oxytocin receptor in the rat, did not antagonize the effect of vasopressin and oxytocin, showing that the oxytocin receptor is not involved in the response. In conclusion, these results suggest that V_{1A} receptor stimulation is responsible for the vasoconstricting effects of both vasopressin and oxytocin in small diameter resistance arteries from the rat uterus.

Keywords: Uterine resistance artery; SR 49059; Atosiban; Oxytocin receptor; Vasopressin receptor

1. Introduction

The hypothalamic–hypophyseal hormones arginine[8]–vasopressin and oxytocin have significant effects in controlling myometrial activity and blood flow in both pregnant and non-pregnant uterus. Both oxytocin and vasopressin V_{1A} receptors have been described in the uterus of several species, including the human (Zingg, 1996; Bossmar et al., 1997). Recent studies have also shown that oxytocin, like vasopressin, has a potent constricting effect in uterine arteries from humans (Ekesbo et al., 1991; Jovanovic et al., 1997) and guinea pigs (Jovanovic et al., 1998). Thus, in addition to regulating normal uterine function, both hormones, by producing uterine ischemia, might be involved in the pathogenesis of primary dysmenorrhea (Åkerlund, 1993; Åkerlund et al., 1995)

The receptor involved in the response of vasopressin and oxytocin in rat uterine artery is not fully defined. It is known that both hormones can interact with either receptors, albeit with different affinity (Zingg, 1996). Therefore, we have characterized the effects of oxytocin and vasopressin in isolated resistance arteries (diameter, 90–120 μm) from non-pregnant rat uteri using two potent and selective receptor antagonists, SR 49059 (Serradeil-Le Gal et al., 1993; Bax et al., 1995), a selective vasopressin V_{1A} antagonist, and atosiban (Maggi et al., 1994; Phaneuf et al., 1994), a selective antagonist of oxytocin at the rat receptor. The isolated resistance artery preparation allowed us to examine the effects of the hormones in the absence of influences from the autonomic nervous system, from contraction/relaxation of the myometrium, and from interactions with other autocoids.

2. Materials and method

2.1. Preparation of uterus strips and tail artery rings

Non-pregnant female and male Sprague–Dawley rats (150–200 g) were obtained from Charles River Labs

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(Kingston, NY). The uteri removed from diethylstilbestrol (0.25 mg/kg, s.c.) treated, pentobarbital-overdosed animals, were cleaned of adhering tissue, cut into 2–3 cm segments, and mounted in organ bath containing de Jalon solution of the following compositions (mM): NaCl, 151.9; KCl, 35.4; $NaHCO_3$, 6.03; $CaCl_2$, 0.04 and glucose, 2.81. The bath was kept at 30°C and aerated with 95% O_2 and 5% CO_2. The tail artery was removed from pentobarbital-overdosed male rats and placed in Krebs solution of the following compositions (mM): NaCl, 112.9; KCl, 4.7; KH_2PO_4, 1.2; $MgSO_4 \cdot 7H_2O$, 1.2; $NaHCO_3$, 25; $CaCl_2$, 2.4 and glucose, 11.5. The artery was cut into 2–3 mm ring segment and mounted in organ bath containing Krebs at 37°C. Tissues were suspended under an initial tension of 1 g and equilibrated for 60 min, while the bathing solution was exchanged at 20–30 min intervals. Mechanical responses were monitored with a force-displacement transducer coupled to a Grass (Model 7) polygraph recorder (Grass Instrument, Quincy, MA).

2.2. Preparation of uterine resistance arteries

Uterine horns were pinned to the bottom of a siliconized Petri dish containing ice-cold MOPS (3-[*N*-morpholino]propanesulfonic acid)-buffered physiologic salt solution of the following compositions (mM): NaCl, 145; KCl, 5.0; $CaCl_2$, 2.0; $MgSO_4$, 1.0; NaH_2PO_4 1.0; dextrose, 5.0; pyruvate, 2.0; EDTA, 0.02 and MOPS, 3.0. Under dissecting scope, segments (1–2 mm in length) of small radial arteries (90–120 μm in diameter) were dissected free from the approximate midpoint of the uterine arterial arcade and transferred to a microvessel chamber containing bicarbonate-buffered Krebs solution (KPSS) at room temperature. The proximal end of the artery was cannulated with a glass micropipette (approximately 50 μm outside diameter) prepared from Prism™ glass capillary (O.D. 1.2 mm, I.D. 0.6 mm, Dagan, Minneapolis, MN) on a microelectrode puller (Sutter Instrument, Novato, CA). After flushing out any residual blood within the vessel, the distal end was cannulated with a second micropipette. Both ends were secured with 11-0 nylon sutures. The KPSS used for the superfusion of the artery contained (mM): NaCl, 110; KCl, 5; $CaCl_2$, 2.5; $MgSO_4$, 1.0; KH_2PO_4, 1.0; glucose, 10; $NaHCO_3$, 24; and EDTA, 0.02, and was saturated with 21% O_2–5% CO_2 and balanced with N_2. Studies in isolated microvessels have indicated that increasing O_2 tension above physiological level produces a progressive vasoconstriction (Messina et al., 1994). For this reason, we used a gas mixture containing 21% O_2, rather than 95%, for the studies with uterine resistance arteries. The temperature of the circulating KPSS was maintained at 37°C and the pH was 7.4. All drugs were added from concentrated stock solutions into an in-line reservoir. Transmural pressure in the artery was set at 75 mm Hg and maintained constant by a pump controlled by a feed-back system. Arterial luminal diameter was continuously measured with a video dimension analyzer (Living Systems Instrumentation, Burlington, VT) and recorded with a computer data acquisition system (Dataq Instruments, Akron, OH).

2.3. Experimental protocol

Preparations were equilibrated for 1 h to develop a stable myogenic tone. After equilibration, the arteries were tested for their capacity to constrict in response to phenylephrine (1×10^{-7} M) and to dilate in response to acetylcholine (1×10^{-7} M). Vessels that did not respond to these agents had probably been injured during the dissection and were deemed unsuitable for this study.

In tail and uterine arteries as well as myometrial preparations, cumulative concentration–response curves for vasopressin or oxytocin were obtained by step-wise addition of increasing concentrations of the agonists after the previous addition had reached steady-state response, or after 5 min, if no measurable response had occurred. As a time-control, cumulative concentration–response curves for each agonist were repeated a second time after 1 h. The second series of concentration–response curves was not significantly different from the first series (see Section 3). Following several washout cycles, when the preparations had returned to their pretreatment diameter or tension, the tissues were incubated for 30 min with either SR 49059 (1×10^{-8} to 1×10^{-7} M) in tail and uterine arteries, atosiban (1×10^{-9} to 1×10^{-8} M) in uterus or atosiban (1×10^{-7} M) for uterine artery only, and the concentration–response curves were repeated in presence of the antagonist.

2.4. Calculation of EC_{50} and pA_2 values, and statistical analysis

For uterine arteries, the responses for each concentration of the agonists is reported as percent change from the pre-drug diameter. For tail artery and uterus preparations, the response for each concentration of the agonists is reported as percent change from the maximal contraction produced by the agonist. The EC_{50} values from the concentration–response curves were obtained by fitting the data to a non-linear logistic regression model using the JMP statistical software package (SAS Institute, Cary, NC). For each concentration of the antagonist, a value for the concentration ratio was calculated by dividing the value of the EC_{50} obtained in the presence of the antagonist by that obtained in its absence. A pA_2 value was obtained from the intercept of the regression line with the abscissa (Arunlakshana and Schild, 1959) using the GraphPad Prism software program (San Diego, CA). EC_{50} and pA_2 values were compared using the *Z*-test (Steel and Torrie, 1980). Results are reported as mean ± S.E.M.

2.5. Drugs

SR 49059 was synthesized by the Resynthesis Laboratory, Wyeth-Ayerst Research. Atosiban [(Deamino-Cys[1], D-Tyr(Et)[2], Thr[4], Orn[8])-Oxytocin] was purchased from Bachem California (Torrance, CA). Arg[8]–vasopressin acetate and oxytocin acetate were from Sigma (St. Louis, MO). All the physiological salts used were of analytical grade and were purchased from J.T. Baker (Philipsburg, NJ).

3. Results

3.1. Vasopressin and oxytocin contract rat isolated uterine resistance arteries

Vasopressin (1×10^{-10} to 1×10^{-7} M) and oxytocin (1×10^{-10} to 1×10^{-7} M) induced a concentration-dependent constriction of isolated rat uterine resistance arteries, with $EC_{50} = 0.44 \pm 0.02$ nM ($n = 8$) for vasopressin and $EC_{50} = 25 \pm 3.1$ nM ($n = 8$) for oxytocin (Fig. 1). Oxytocin and vasopressin had similar maximum efficacy producing total vessel occlusion, but vasopressin was 57-fold more potent than oxytocin. Repeated exposure to both agonists 1 h after the first exposure still produced total vessel occlusion with EC_{50} values of 0.46 ± 0.02 nM and 22 ± 1.9 nM for vasopressin and oxytocin, respectively. These values were not significantly different from the controls, indicating absence of tissue desensitization.

Conceivably, the vasoconstriction could depend on stimulation of vasopressin V_{1A} or oxytocin receptors by each agonist, or both. In addition, it is well known that in several tissues vasopressin shows high affinity for oxytocin receptors and that oxytocin shows a lower but measurable affinity for the V_{1A} receptor (Guillon et al., 1987; Zingg, 1996). To examine the role of each receptor, we further examined the effects of SR 49059 (Serradeil-Le Gal et al., 1993; Bax et al., 1995), a non-peptidic vasopressin V_{1A} receptor antagonist, and atosiban (Maggi et al., 1994; Phaneuf et al., 1994), a selective antagonist of oxytocin at the rat receptor.

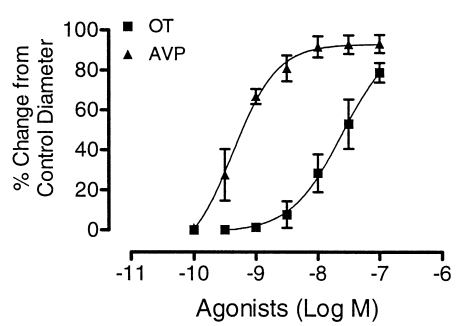
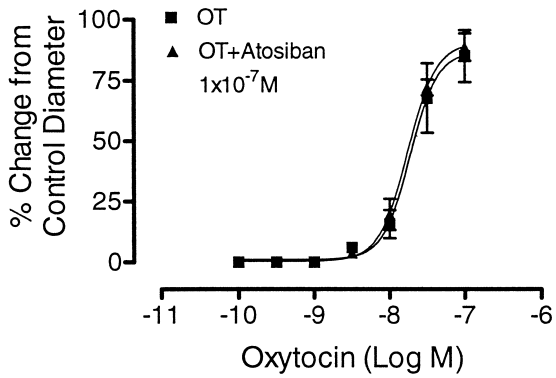


Fig. 1. Concentration–response curves for vasopressin and oxytocin in isolated rat uterine resistance arteries. Vasopressin and oxytocin induced a concentration-dependent constriction with a similar maximum effect (i.e., total vessel occlusion). The EC_{50} was 0.44 ± 0.02 and 25 ± 3.1 nM for vasopressin and oxytocin, respectively. Symbols represent the mean ± S.E.M. of eight preparations.



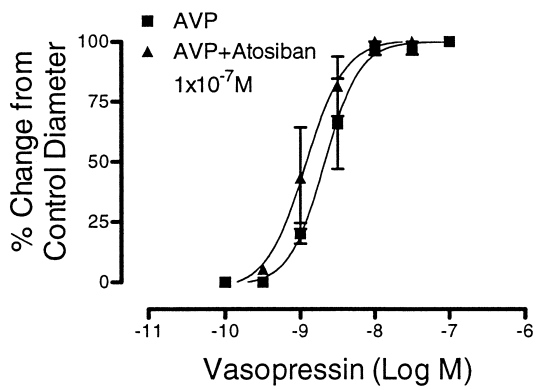


Fig. 2. Lack of antagonism for oxytocin- and vasopressin-induced constriction in isolated rat uterine resistance arteries before and after atosiban, a selective antagonist of oxytocin receptor in the rat. Symbols represent the mean ± S.E.M. of three preparations.

3.2. Atosiban fails to inhibit the vasoconstricting effects of vasopressin and oxytocin

The oxytocin antagonist atosiban (1×10^{-7} M) did not affect the basal diameter of isolated resistance uterine arteries and failed to antagonize the vasoconstricting effects of either oxytocin or vasopressin (Fig. 2). These results clearly suggest that stimulation of oxytocin receptors is not responsible for the vasoconstriction.

3.3. SR 49059 inhibits the vasoconstricting effects of vasopressin and oxytocin

SR 49059, a selective non-peptide antagonist of vasopressin at V_{1A} receptors did not alter the basal diameter of isolated resistance uterine arteries but caused a parallel shift to the right of both the vasopressin and oxytocin (Fig. 3) concentration–response curves without reducing the maximum effect of either agonists. These results are indicative of a competitive antagonism and yielded a pA_2

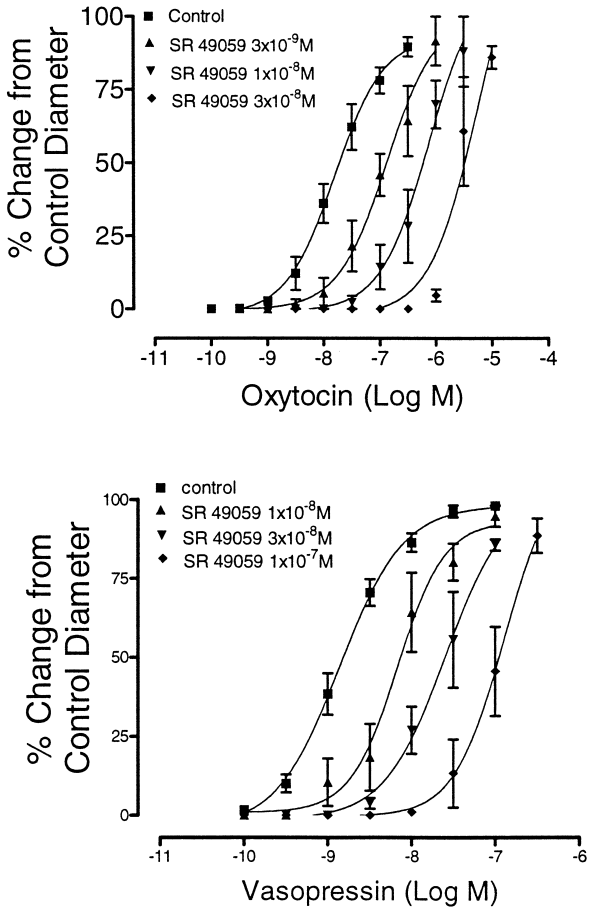


Fig. 3. Antagonism of vasopressin- and oxytocin-induced constriction by SR 49059 in isolated rat uterine resistance arteries. SR 49059 antagonized the effect of vasopressin and oxytocin yielding pA_2 values of 8.96 ± 0.60 and 9.06 ± 0.23, respectively. Symbols represent the mean $\pm$ S.E.M. of 5–7 preparations.

value of 8.96 ± 0.60 with vasopressin and 9.06 ± 0.23 with oxytocin. With either agonist, the slopes of the Schild plots were not significantly different from unity (Table 1), consistent with the hypothesis of competitive antagonism. Furthermore, the pA_2 values with either agonist were not significantly different, which is consistent with the hypothesis that both agonists stimulated the same receptor. The antagonism observed with SR-49059, together with the lack of effects with atosiban, clearly suggest that both vasopressin and oxytocin produce vasoconstriction of resistance uterine arteries by stimulation of vasopressin V_{1A} receptors.

3.4. Antagonistic effects of atosiban and SR-49059 in isolated rat tail artery and uterus preparations

To examine the selectivity of atosiban and SR 49059, we studied their effects against vasopressin- and oxytocin-induced contractions in standard and well characterized pharmacological preparations that express oxytocin and V_{1A} receptors. Vasopressin produced a concentration-dependent contraction of rat tail artery (Fig. 4A and C) and oxytocin produced a concentration-dependent contraction of uterus myometrial strips (Fig. 4B and D). The EC_{50} values were 1.59 ± 0.02 nM ($n = 15$) for vasopressin in the tail artery and 8.81 ± 0.47 nM ($n = 26$) for oxytocin in the uterus. The EC_{50} values following a second exposure to each agonist 1 h after the first were 1.50 ± 0.16 nM for vasopressin and 8.2 ± 0.14 nM for oxytocin, indicating a lack of tissue desensitization. Both SR 49059 and atosiban behaved as competitive antagonists but showed different selectivity. SR 49059 yielded a pA_2 value of 9.27 ± 0.11 against vasopressin in the tail artery (Fig. 4A) and 8.10 ± 0.16 against oxytocin in the uterus (Fig. 4B), indicating high affinity for both receptors and a modest 10-fold selectivity for the V_{1A} receptor. On the other hand, atosiban yielded a pA_2 value of 5.63 ± 0.08 against vasopressin in the tail artery (Fig. 4C), and 9.10 ± 0.10 against oxytocin in the uterus (Fig. 4D), showing an almost 3000-fold selectivity for the oxytocin receptor. The pA_2 values and the associated slopes from the Schild analysis are summarized in Table 1.

To further characterize the selectivity of both antagonists, we studied their effects against vasopressin in uterine strips. Both compounds behave as competitive antagonists with pA_2 values of 8.21 ± 0.06 for SR 49059 and 9.33 ± 0.13 for atosiban. These results are also included in Table 1. In a separate series of studies, we also examined the vasoconstricting effects of oxytocin in rat tail artery. Oxytocin did produce a concentration-dependent contraction,

Table 1
The pA_2 values of SR 49059 and atosiban against vasopressin and oxytocin. ND = not determined

Antagonist	Agonist				Tissue
	Vasopressin		Oxytocin		
	pA_2	Slope	pA_2	Slope	
SR 49059	8.96 ± 0.60	1.06 ± 0.12	9.06 ± 0.23	1.01 ± 0.29	uterine artery
SR 49059	8.21 ± 0.06	0.85 ± 0.27	8.10 ± 0.16	0.89 ± 0.13	uterine strip
Atosiban	9.33 ± 0.13	0.71 ± 0.11	9.10 ± 0.10	0.92 ± 0.13	uterine strip
SR 49059	9.27 ± 0.11	1.09 ± 0.08	ND	ND	tail artery
Atosiban	5.63 ± 0.08	0.86 ± 0.07	ND	ND	tail artery

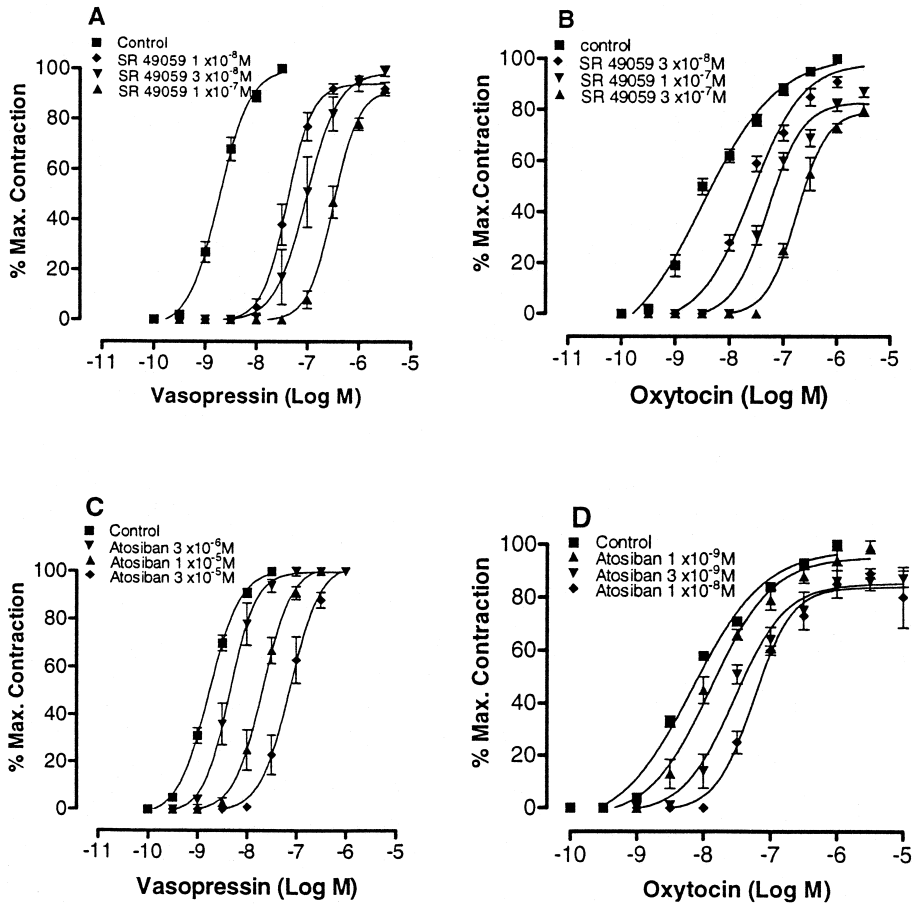


Fig. 4. Antagonistic effects of SR 49059 and atosiban against vasopressin in tail artery (A and C) and against oxytocin in rat uterus (B and D). SR 49059 yielded pA_2 values of 9.27 ± 0.11 against vasopressin and 8.10 ± 0.16 against oxytocin. Symbols represent the mean $\pm$ S.E.M. of 3–6 preparations. Atosiban yielded pA_2 values of 9.10 ± 0.10 against oxytocin and 5.63 ± 0.08 against vasopressin. Symbols represent the mean $\pm$ S.E.M. of 5–8 preparations.

but was much less potent than in isolated uterine resistance arteries, yielding an EC_{50} value of approximately 1 μM (data not shown), and almost 1000-fold less potent than vasopressin in the tail artery preparation. Because of the low potency, we did not further characterize the selectivity of atosiban and SR 49059 against oxytocin in this preparation.

4. Discussion

Several studies, both in vivo and in vitro, have examined the vascular effects of vasopressin and oxytocin on arteries from uterus (Ekstrom et al., 1991; Jovanovic et al., 1997), gastrointestinal tract (Vanner et al., 1990; Calo et al., 1997), brain (Suzuki et al., 1992; Tagawa et al., 1993), heart (Bax et al., 1995), kidney (Barthelmebs et al., 1996) and extraocular muscles (Okamura et al., 1997). Most of the in vitro studies observed changes of tension induced by the either agonist on vascular preparation removed from main stem to medium-sized arteries (diameter from 400 to 1000 μm). Our study describes the effects of oxytocin and vasopressin in rat uterine resistance arteries whose diameter ranged from 90 to 120 μm. Small diameter arteries and arterioles constitute the major resistance to end-organ blood flow, and thus have the greatest influence on the blood flow to the uterus.

Vasopressin and oxytocin evoked a potent concentration-dependent vasoconstriction of isolated resistance arteries from the rat uterus with EC_{50} values of 0.44 and 25 nM, respectively. Notably, oxytocin was a much less potent contractor in the isolated tail artery showing an EC_{50} of about 1 μM (data not shown). These results are in agreement with previous studies, in that: (a) both hormones have potent vasoconstricting effects in uterine arteries, and (b) vasopressin is a more potent constrictor than oxytocin (Ekstrom et al., 1991; Jovanovic et al., 1997). Surprisingly, both vasopressin and oxytocin can induce vasodilatation in different blood vessels from several species. For example, vasopressin can elicit relaxation in isolated canine short posterior ciliary arteries (Okamura et al., 1997), in human forearm vessels (Tagawa et al., 1993) and in the dog peripheral circulation (Liard, 1994). The relaxation was abolished or inhibited by endothelium re-

moval or pretreatment with the nitric oxide synthase inhibitors L-NNA (N^G-nitro-L-arginine), L-NAME (N^W-nitro-L-arginine methyl ester) and *l*-NMMA (N^G-monomethyl-L-arginine). In the canine brain circulation, oxytocin caused an endothelium-dependent relaxation that was competitively inhibited by V_{1A} antagonist (Katusic et al., 1986; Suzuki et al., 1992). In our study in rat uterine vessels, we did not observe any vasodilatory responses to either vasopressin or oxytocin at any concentration tested.

Using rat uterus and tail artery preparations, we report that atosiban is approximately 3000-fold more selective for oxytocin than for vasopressin receptors, based on a pA_2 value of 9.10 (uterus) and 5.63 (tail artery). Atosiban (1×10^{-7} M), a concentration 100-fold higher than its pA_2 values for oxytocin receptors, failed to produce any changes in the concentration–response curves of oxytocin and vasopressin in uterine resistance arteries, strongly suggesting that stimulation of oxytocin receptors does not contribute to the vasoconstriction observed with these peptides. Of some interest, the high selectivity of atosiban for the V_{1A} receptor observed seems to be tissue- and species-dependent (Phaneuf et al., 1994). In human tissues (liver and uterus), atosiban shows higher affinity for the vasopressin V_{1A} receptor (Pettibone et al., 1992). In our studies in uterine strips contracted with vasopressin, the high value of pA_2, (i.e., 9.33) is consistent with a high affinity for the V_{1A} receptor.

SR 49059 is a potent V_{1A} receptor antagonist. The pA_2 value of 9.42 reported in the vasopressin-induced contraction of rat caudal artery (Serradeil-Le Gal et al., 1993) is comparable to the value of 9.27 obtained in the present study. However, we only saw a modest 10-fold selectivity for the V_{1A} over the oxytocin receptor in uterine strips ($pA_2 = 8.10$). This latter value is also very close to the pA_2 value of 8.21 obtained against vasopressin in the same preparation. In contradistinction, previous binding studies employing rat tissue (liver and mammary gland) showed a high degree of selectivity (two orders of magnitude or higher) for the V_{1A} over the oxytocin receptor (Serradeil-Le Gal et al., 1993). The reason for this discrepancy is unclear. In any case, in the small diameter rat uterine artery, SR 49059 produced a competitive inhibitions of the vasoconstrictions induced by both vasopressin and oxytocin, yielding pA_2 values of 8.96 and 9.06, respectively. These values are not significantly different, suggesting that the vasoconstriction observed with both hormones is mediated by the same type of receptors, that is, by vasopressin V_{1A} receptors.

Myometrial hypercontractility and decreased blood flow to the uterus are thought to be causative factors in the symptoms of primary dysmenorrhea. (Åkerlund, 1987; Åkerlund, 1993). In particular, vasoconstriction of small uterine arteries by vasopressin and oxytocin is thought to produce tissue ischemia and pain. Recent studies in human and guinea pig uterine arteries have shown that both hormones have potent vasoconstricting effects (Ekesbo et al., 1991; Jovanovic et al., 1997, 1998) through activation of vasopressin V_{1A} receptors. Our results in rat uterine arteries indicate that V_{1A} but not oxytocin receptor antagonism can block the vasoconstricting effects of both oxytocin and vasopressin, indicating that V_{1A} receptor stimulation is responsible for the vasoconstriction.

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