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Relaxant Effect of Oxytocin on Isolated Human Oviduct

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Aim. Oxytocin produces concentration-dependent relaxation of isolated isthmus and ampulla of human oviduct precontracted by histamine. The aim of our study was to investigate whether this oxytocin effect was specific and by which receptors it was mediated.

Methods. We investigated effects of oxytocin and its antagonists on isolated isthmus and ampulla of the uterine tubes from 20 women who underwent surgery for uterine fibroids. Selective vasopressin and oxytocin antagonists were used to treat isolated preparations of the tubes.

Results. In a concentration-dependent manner, oxytocin enhanced spontaneous relaxation of both isthmus (EC_{50} = 1.23±0.03x10^{-7} mol/L) and ampulla (EC_{50} = 1.04±0.26x10^{-7} mol/L) precontracted by histamine. Neither predominantly selective vasopressin V_1 receptor antagonist, [β-mercapto-β,β-cyclopentamethylene-propionyl1,0-metyr2,arg8]-vasopressin (1.0x10^{-9}-1.0x10^{-7} mol/L), nor predominantly selective vasopressin V_2 antagonist, [1-(β-mercapto-β,β-cyclopentamethylene-propionic acid), 2-D-isoleucine, 4-D-isoleucine]-arginine-vasopressin (1.0x 10^{-9}-1.0x10^{-7} mol/L) affected significantly the relaxation of isolated ampulla and isthmus produced by oxytocin. On the other hand, [Deamino-Cys^1,D-Tyr (Et)^2, Thr^4, Orn^8]-oxytocin, a selective blocker of oxytocin receptors, produced in a concentration-dependent manner (6.7x10^{-9} mol/L, 2.0x10^{-8} mol/L, and 6.7x10^{-7} mol/L) significant shifts of the concentration-response curves of relaxation for oxytocin to the right in isolated preparations of both the ampulla and the isthmus. The values of pA_2 for [Deamino-Cys^1,D-Tyr (Et)^2, Thr^4, Orn^8]-oxytocin calculated from constrained Schild's plot were 8.08±1.53 for ampulla and 7.94±0.67 for isthmus.

Conclusion. Oxytocin relaxes smooth muscles in human oviduct through a specific effect on oxytocin receptors.

Key words: *Fallopian tubes; muscle, smooth; oxytocin; receptors, oxytocin; uterine diseases*

Oxytocin and vasopressin are more likely to produce contractions than relaxation in vascular and extravascular smooth muscles. Some of the smooth muscles that relax under the influence of these neurohypophyseal hormones are canine cerebral and basilar arteries, guinea pig and human gallbladder, and guinea pig gastric antrum and human oviduct. The latter are relaxed only by oxytocin (1-4). Receptors for oxytocin are present in smooth muscle cells of the isthmic and ampullary segments of the human oviducts (5-7). The expression of receptors in the isthmic segment is increased especially during the early secretory phase of the menstrual cycle (8,9). Treatment with estrogens increases the number of oxytocin receptors and enhances their responsiveness to oxytocin (10). In anestrous ewes treated with estrogens, oxytocin increases the electromyographic activity of ampullary -isthmic junction (11). Vasopressin receptors also exist in the tubal smooth muscle cells. These are in the V_1 isoform (12).

Regarding the post-receptor modulation of oxytocin relaxant action, it has been shown that activation of oxytocin receptors on smooth muscle cells in guinea-pig gastric antrum was followed by phosphatidylinositol hydrolysis, formation of inositol 1,4,5-trisphosphate, and release of Ca^{2+} from the submembrane-located cisternae of the sarcoplasmic reticulum (13). Increased intracellular calcium causes opening of Ca^{2+}- sensitive K^+ channels in the plasmalemmal membrane, its hyperpolarization, and smooth muscle cell relaxation (4).

There are three types of vasopressin (V_1 – vascular, V_2 – renal, and V_3 – hypophyseal) and one type of oxytocin receptors. They are all present in outer membranes of target cells and coupled to G-proteins (14). In our previous study (2), oxytocin had a relaxant effect of on the human oviduct, whereas vasopressin was ineffective. The aim of the present study was to investigate whether this effect of oxytocin was mediated through oxytocin receptors.

Material and Methods

Specimens

Uterine tubes were taken from 20 women (one tube from each patient) who underwent abdominal hysterectomy with adnexectomy because of extensive uterine fibroids, which were causing prolonged uterine bleeding. The patients were unable to identify regular menstrual bleeding for 3 months prior to hospital admission. The mean age of the women was 45.1±4.4 years (range, 38-53 years). All patiens gave

their informed consent before the surgery for the specimens taken from their adnexa to be used in this research.

All patients underwent surgery between 1999 and 2000 at the Gynecology Department of Kragujevac University Hospital Center, FR Yugoslavia. It took 18 months to collect the samples due to difficulties in obtaining undamaged samples of the same size. The patients had not been taking sex hormones during two months before the operation. They underwent surgery under general anesthesia with N_2O, fentanyl, and droperidol. The anesthesia was induced by intravenous injection of thiopentone sodium, and muscle relaxation was achieved initially by succinylcholine and then by pancuronium. All patients were premedicated with 0.5 mg of atropine subcutaneously.

After clamping the blood vessels, the uterine tube was resected and placed in 250 mL dish filled with De Jalons solution (NaCl 9.0 g, $NaHCO_3$ 0.5 g, glucose 0.5 g, KCl 0.42 g, and $CaCl_2x2H_2O$ 0.06 g in a liter of solution), which was gassed (95% O_2 and 5% CO_2, 5 mL/min), and transported to the laboratory.

Isolated Preparations

Within 15 min after resection, the preparations of uterine tubes were mounted in an isolated organ bath. Two types of uterine tube preparations were isolated: isthmus and ampulla. The serosa was removed from both. The isthmus preparations used in the experiments were 4 cm long, with wall thickness of 1.3 mm, and the lumen diameter of 1 mm. Ampullary preparations used in the experiments were 5 cm long, with wall thickness of 1.2 mm, and the lumen diameter of 6 mm. Both types of preparations were mounted in an organ bath longitudinally, analogous with Magnus preparations of the rat ileum (15).

The isolated preparations were mounted in 15 mL isolated organ bath filled with De Jalons solution. The bath solution was maintained at 37°C and aerated with 95% O_2 and 5% CO_2. One end of the isolated preparation was attached to the bath base, and the other to the lever of the isotonic transducer (T_3 isotonic transducer, Palmer Bio Science, Los Angeles, CA, USA). Preparations were placed under a load of 0.5 g. Tonic contractions of isolated preparations were recorded on Linseis recorder, model L6522 (Selb, Germany).

Agonists and Antagonists

After being placed in isolated organ bath, the preparations were allowed 45 min to equilibrate.

The preparations were contracted by $3.62x10^{-4}$ mol/L histamine and left for 3 min to obtain the plateau of histamine contraction and start spontaneous relaxation.

Oxytocin was then added cumulatively (5 to 8 doses of oxytocin added subsequently per cumulation, without bath washings in-between) to the bath 3 min after the isolated preparations were contracted by histamine. The effect of each dose of oxytocin was recorded until it reached the plateau. At least 45 min would elapse between two oxytocin cumulations.

The antagonists were added to the bath 20 min before the histamine dose. The effect of each concentration of histamine, oxytocin, or the antagonists was recorded in at least 4 different preparations from 4 different patients.

Chemicals

The following substances were used: histamine dihydrochloride (Sigma Chemical Co., St. Louis, MO, USA), oxytocin (Sandoz, Bern, Switzerland), [(Deamino-Cys^1,D-Tyr $(Et)^2$, Thr^4, Orn^8)]-oxytocin (Bachem, Bubendorf, Germany), (β-mercapto-β, β-cyclopentamethylene-propionyl1,o-me-tyr2, arg8)-vasopressin (Sigma), and [1-(β-mercapto-β,β-cyclopentamethylene-propionic acid), 2-D-isoleucine, 4-D-isoleucine] arginine-vasopressin (Bachem).

Statistics

The relaxation induced by each oxytocin concentration was expressed as a percentage of the maximum relaxation induced by oxytocin and used for construction of concentration-response curves. The concentration-response relationship was determined by linear regression calculated according to the method of least squares (16). The concentration of oxytocin eliciting 50% of its own maximum response (EC_{50}) and its confidence limits (1.96 x standard error) were determined graphically for each curve by linear interpolation (17). The pA_2 values (-log molar concentration of antagonist reducing the agonist response by a factor of two) for [(Deamino-Cys^1,D-Tyr $(Et)^2$, Thr^4, Orn^8)]-oxytocin were determined with a Schild plot (18-20). The concentration ratios (the ratio between the EC_{50} value for oxytocin in the presence and absence of an antagonist) at different antagonist concentrations were calculated for each experiment. Thus, the mean values of concentration ratios for an oxytocin/antagonist pair were plotted in a Schild diagram using regression analysis, and pA_2 was obtained from the intercept of the regression line on the abscissa (18,19). The significance of the Schild plot linearity was tested by analysis of variance (17). The difference of the slope to unity was verified by Student's t-test and was found to be significant at $p<0.05$. Thereafter, pA_2 values were calculated from constrained Schild's plot, assuming the slope to be equal to one (21).

The results are expressed as means ±95% confidence intervals. Two-way analysis of variance (two-way ANOVA) was used when two blocks of groups were analyzed (e.g., responses on different concentrations of oxytocin in presence and in absence of an antagonist). Statistical differences between two means were determined by Student's t-test for paired or unpaired observations where appropriate, with $p<0.05$ considered as statistically significant (21).

All calculations were performed by one of the authors (SMJ), either manually or using computer programs written in BASIC by SMJ.

Results

Isolated Preparations of Ampullas

Preparations of the ampullas from all patients showed spontaneous activity comprised of slow phasic contractions with amplitude of 8.7±2.5 μN (n = 20) and frequency of 3 to 5 cycles/min.

Histamine ($3.62x10^{-4}$ mol/L) produced a sustained tonic contraction of all isolated preparations with amplitude 29.8±7.4 μN (n = 20). The contraction reached the plateau after 2 min with an ongoing tendency to decline spontaneously (Fig. 1); 15 min after histamine was added to the bath, the preparations spontaneously relaxed for 33.0±8.7% (n = 20) of original level of the contraction. Histamine did not affect spontaneous contractions.

Oxytocin ($5.7x10^{-8}$-$6.8x10^{-7}$ mol/L) produced concentration-dependent relaxation of all isolated preparations, but the maximal relaxation was too small to be analyzed (below 7.4 μN). In the same concentration range and in a concentration-dependent manner, oxytocin enhanced spontaneous relaxation (Fig. 1A) of all isolated preparations previously contracted by histamine ($p\leq0.05$). Maximal extent of oxytocin- induced relaxation was 17.1±2.5 μN (spontaneous relaxation subtracted; n = 20). EC_{50} for oxytocin was $1.04\pm0.26x10^{-7}$ mol/L (regression line equation: $y = 57.3x - 56.5$; $t = 9.30$, $df = 18$, $p<0.001$; $r = 0.9106$). Oxytocin did not affect spontaneous contractions of the isolated preparations.

Neither predominantly selective vasopressin V_1 receptor antagonist (β-mercapto-β,β-cyclopentamethylene- propionyl1,o-me-tyr2, arg8)-vasopressin ($1.0x10^{-9}$-$1.0x\ 10^{-7}$ mol/L) nor predominantly selective vasopressin V_2 antagonist [1-(β-mercapto-β,β-cyclopentamethylene- propionic acid), 2-D-isoleucine,4-D-isoleucine]arginine- vasopressin ($1.0x10^{-9}$- $1.0x10^{-7}$ mol/L) significantly affected the relaxation of isolated ampulla produced by oxytocin, e.g., the highest concentration of predominantly selective V_1 receptor antagonist did not shift concentration-response curve for oxytocin at all (control $EC_{50} = 1.01\pm0.01x10^{-7}$ mol/L vs $EC_{50} = 1.02\pm0.02x10^{-7}$ mol/L in the presence of V_1 antagonist; $t = 0.05$, $df = 31$, $p>0.05$; $F = 0.04$, $df = 1$,

$p > 0.05$), and the same was observed with the highest concentration of predominantly selective V_2 receptor antagonist (control $EC_{50} = 1.23 \pm 0.01 \times 10^{-7}$ mol/L vs $EC_{50} = 1.28 \pm 0.02 \times 10^{-7}$ mol/L in the presence of V_1 antagonist; $t = 0.81$, $df = 28$, $p > 0.05$; $F = 0.24$, $df = 1$, $p > 0.05$).

On the other hand, selective blocker of oxytocin receptors [(Deamino-Cys^1,D-Tyr (Et)^2, Thr^4, Orn^8)]-oxytocin produced significant shifts of the concentration-response curve of relaxation for oxytocin to the right in a concentration-dependent manner (for the concentration of 6.7×10^{-9} mol/L: $t = 2.40$, $df = 42$, $p < 0.05$; and $F = 1.69$, $df = 1$, $p > 0.05$; for the concentration of 2.0×10^{-8} mol/L: $t = 8.58$, $df = 47$, $p < 0.001$, and $F = 22.26$, $df = 1$, $p < 0.001$; for the concentration of 6.7×10^{-7} mol/L: $t = 10.80$, $df = 50$, $p < 0.001$ and $F = 66.83$, $df = 1$, $p < 0.001$) (Fig. 2). The data from the experiments with oxytocin receptor antagonist were analyzed as described by Arunlakshana and Schild (19). The antagonist yielded straight line ($y = -2{,}19x + 17.27$; $r = 0.991$) with slope of 2.2, and pA_2 value of 7.86±0.77 (n = 3) (Fig. 3). The 95% confidence limits were the following: for slope -5.98 (lower) and 1.59 (upper), and for y-intercept -11.89 (lower) and 46.42 (upper). Since the slope was far from the accepted value for competitive antagonists (0.9 to 1.1), the pA_2 value of 8.08±1.53 was calculated from constrained Schild's plot (SEM = 0.77; n = 4).

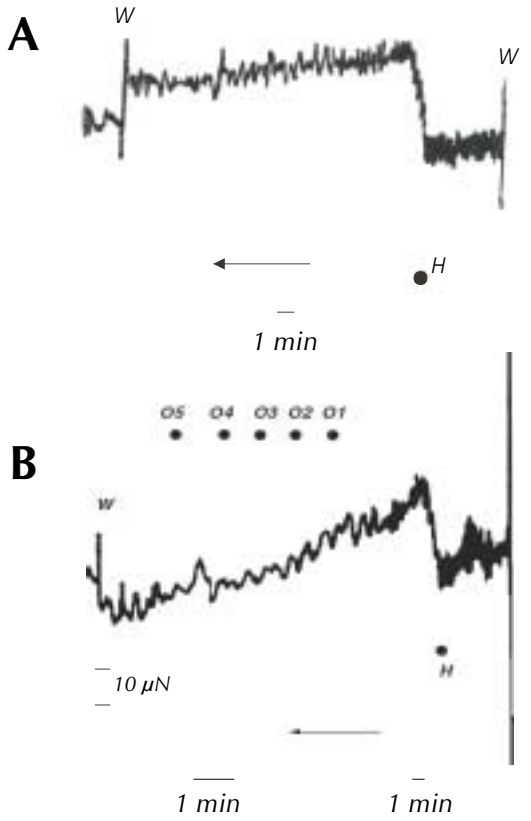

Figure 1. A. Experimental recording of the histamine ($3{,}62 \times 10^{-4}$ mol/L) effect on the isolated ampulla from human uterine tube. **B.** Experimental recording of relaxation of the isolated ampulla from human uterine tube induced by oxytocin. The preparation was pre-contracted by histamine ($3{,}62 \times 10^{-4}$ mol/L). Concentrations of oxytocine achieved in isolated organ bath at marked points: $O1 = 5{,}7 \times 10^{-8}$ mol/L; $O2 = 1.7 \times 10^{-7}$ mol/L; $O3 = 2.83 \times 10^{-7}$ mol/L; $O4 = 4.53 \times 10^{-7}$ mol/L; $O5 = 6{,}8 \times 10^{-7}$ mol/L. The arrow points to the direction of the recording. Three min after adding histamine to the bath, the recording velocity reached 10 cm/h, and later 40 cm/h. H – histamine added to the organ bath; W – washing of the organ bath.

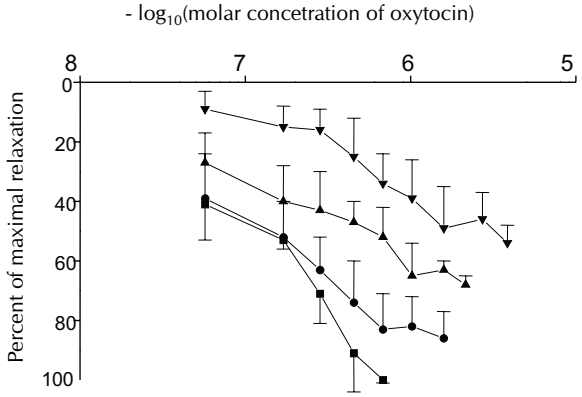

Figure 2. Effects of selective blocker of oxytocin receptors [(Deamino-Cys^1,D-Tyr (Et)^2, Thr^4, Orn^8)]-oxytocin (6.7×10^{-9} mol/L, 2.0×10^{-8} mol/L, and 6.7×10^{-7} mol/L) on oxytocin-produced relaxations of ampullar segment of uterine tubes taken from the patients with uterine fibroids. Each point is mean response of isolated preparations from four different patients (the measurement of the response of the preparation from each patient was made once). Error bars – standard deviations. Square – oxytocin-control; circle – oxytocin + 6.7×10^{-9} mol/L of [(Deamino-Cys^1,D-Tyr (Et)^2, Thr^4, Orn^8]-oxytocin; triangle – oxytocin + 2.0×10^{-8} mol/L of [(Deamino-Cys^1, D-Tyr (Et)^2, Thr^4, Orn^8]-oxytocin; reversed triangle – oxytocin + 6.7×10^{-7} mol/L of (Deamino-Cys^1,D-Tyr (Et)^2, Thr^4, Orn^8)]-oxytocin.

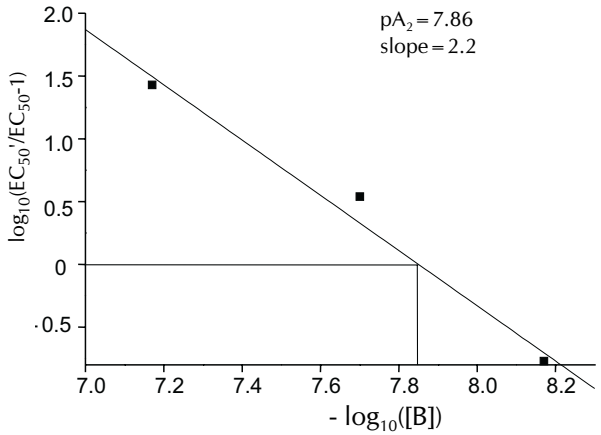

Figure 3. Schild's plot of [(Deamino-Cys^1,D-Tyr (Et)^2, Thr^4, Orn^8)]-oxytocin blocking effect on relaxations of isolated ampulla produced by oxytocin. [B] – molar concentration of the antagonist; EC_{50} – the concentration of oxytocin which produces half of the maximal relaxation in absence of the antagonist; EC_{50}' – the concentration of oxytocin which produces half of the maximal relaxation in the presence of certain concentration of the antagonist.

Isolated Preparations of Isthmus

The isolated preparations of isthmus did not show spontaneous activity. Histamine ($3.62x10^{-4}$ mol/L) produced sustained tonic contraction of isolated preparations with amplitude 42.2±10.4 μN (n = 20). The contraction reached the plateau after 2 min, with ongoing tendency to decline spontaneously (Fig. 4A); 15 min after histamine was added in the bath, the preparations spontaneously relaxed for 24.2±6.2% (n = 20) of the original level of the contraction.

Oxytocin (from $5.7x10^{-8}$ mol/L to $6.8x10^{-7}$ mol/L) produced concentration-dependent relaxation of isolated preparations, but the maximal relaxation was too small to be analyzed (below 7.4 μN). In the same concentration range and in a concentration-dependent manner oxytocin enhanced spontaneous relaxation (Fig. 4B) of the isolated preparations previously contracted by histamine ($p \leq 0.01$). The maximal extent of oxytocin-induced relaxation was 32.2±9.9 μN (n = 17; spontaneous relaxation subtracted). The EC_{50} for oxytocin was 1.23± $0.03x10^{-7}$ mol/L (regression line equation: y = 62.5x –80.9; t = 7.04, df = 18, $p < 0.01$; r = 0.8567).

Neither predominantly selective vasopressin V_1 receptor antagonist (β-mercapto-β,β-cyclopentamethylene-propionyl1,o-me-tyr2, arg8)-vasopressin ($1.0x10^{-9}$-$1.0x10^{-7}$ mol/L) nor predominantly selective vasopressin V_2 antagonist [1-(β-mercapto-β,β-cyclopentamethylene-propionic acid)], 2-D-isoleucine, 4-D-isoleucine]arginine-vasopressin ($1.0x10^{-9}$-$1.0x10^{-7}$ mol/L) affected significantly the relaxation of isolated isthmus produced by oxytocin, e.g., the highest con-

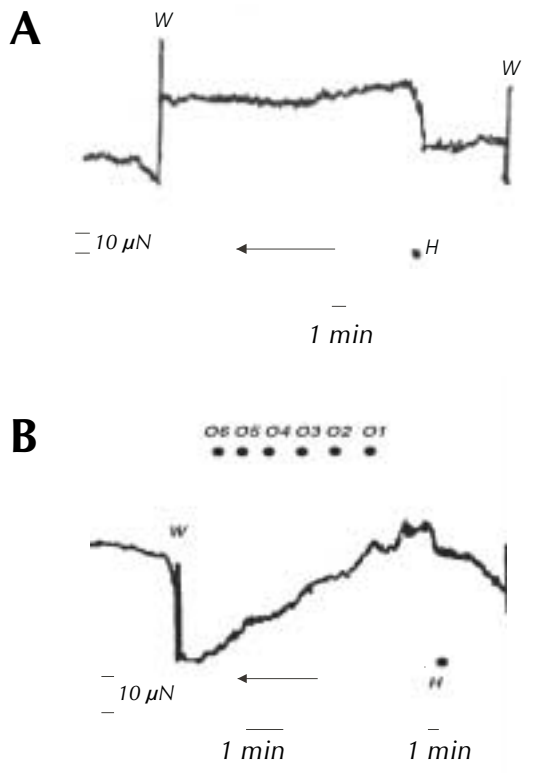

Figure 4. A. Experimental recording of the histamine ($3,62x10^{-4}$ mol/L) effect on the isolated isthmus from human uterine tube. **B.** Experimental recording of relaxation of the isolated isthmus from human uterine tube induced by oxytocin. The preparation was pre-contracted by histamine ($3,62x10^{-4}$ mol/L). Concentrations of oxytocine achieved in isolated organ bath at marked points: 01 = $5,7x10^{-8}$ mol/L; 02 = $1.7x10^{-7}$ mol/L; 03 = $2.83x10^{-7}$ mol/L; 04 = $4.53x10^{-7}$ mol/L; 05 = $6,8x10^{-7}$ mol/L; 06 = $1.02x10^{-6}$ mol/L The arrow points to the direction of the recording. Untill 3 min from adding histamine to the bath elapsed, the recording velocity was 10 cm/h, and later 40 cm/h. H – histamine added to the organ bath; W – washing of the organ bath.

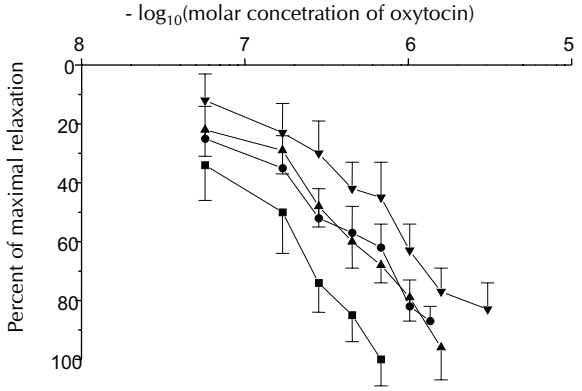

Figure 5. Effects of selective blocker of oxytocin receptors [(Deamino-Cys^1,D-Tyr $(Et)^2$, Thr^4, Orn^8)]-oxytocin ($6.7x10^{-9}$ mol/L, $2.0x10^{-8}$ mol/L, and $6.7x10^{-7}$ mol/L) on oxytocin-produced relaxations of isthmic segment of uterine tubes taken from the patients with uterine fibroids. Each point is mean response of isolated preparations from four different patients (the measurement of the response of the preparation from each patient was made once). Error bars – standard deviations. Square – oxytocin-control; circle – oxytocin + $6.7x10^{-9}$ mol/L of [(Deamino-Cys^1,D-Tyr $(Et)^2$, Thr^4, Orn^8)]-oxytocin; triangle – oxytocin + $2.0x10^{-8}$ mol/L of [(Deamino- Cys^1,D-Tyr $(Et)^2$, Thr^4, Orn^8)]-oxytocin; reversed triangle – oxytocin + $6.7x10^{-7}$ mol/L of [(Deamino-Cys^1,D-Tyr $(Et)^2$, Thr^4, Orn^8)]-oxytocin.

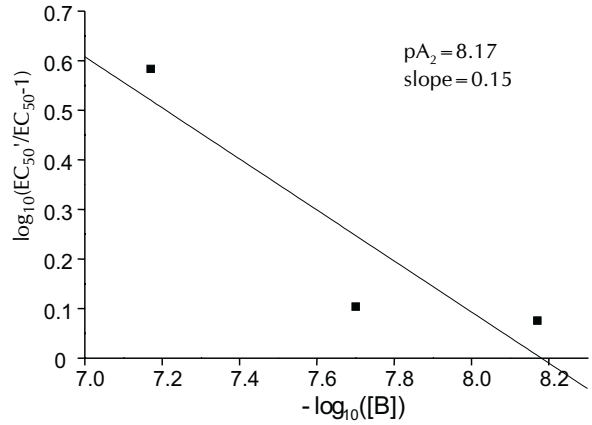

Figure 6. Schild's plot of [(Deamino-Cys^1,D-Tyr $(Et)^2$, Thr^4, Orn^8)]-oxytocin blocking effect on relaxations of isolated isthmus produced by oxytocin. [B] – molar concentration of the antagonist; EC_{50} – the concentration of oxytocin which produces half of the maximal relaxation in absence of the antagonist; EC_{50}' – the concentration of oxytocin which produces half of the maximal relaxation in the presence of certain concentration of the antagonist.

centration of predominantly selective V_1 receptor antagonist caused statistically insignificant shift of concentration-response curve for oxytocin to the left (control $EC_{50} = 1.67 \pm 0.01 \times 10^{-7}$ mol/L vs $EC_{50} = 1.30 \pm 0.02 \times 10^{-7}$ mol/L in the presence of V_1 antagonist; $t = 0.29$, $df = 51$, $p > 0.05$; $F = 0.01$, $df = 1$, $p > 0.05$). The same was observed with the highest concentration of predominantly selective V_2 receptor antagonist (control $EC_{50} = 1.26 \pm 0.01 \times 10^{-7}$ mol/L vs $EC_{50} = 0.25 \pm 0.04 \times 10^{-7}$ mol/L in the presence of V_2 antagonist; $t = 0.70$, $df = 37$, $p > 0.05$; $F = 0.24$, $df = 1$, $p > 0.05$).

On the other hand, selective blocker of oxytocin receptors [(Deamino-Cys^1,D-Tyr (Et)^2, Thr^4, Orn^8)]-oxytocin produced significant shifts of the concentration-response curve of relaxation for oxytocin to the right in a concentration-dependent manner (for the concentration of 6.7×10^{-9} mol/L: $t = 4.81$, $df = 43$, $p < 0.01$ and $F = 9.14$, $df = 1$, $p < 0.01$; for the concentration of 2.0×10^{-8} mol/L: $t = 4.92$, $df = 45$, $p < 0.01$ and $F = 9.30$, $df = 1$, $p < 0.01$; for the concentration of 6.7×10^{-7} mol/L: $t = 5.10$, $df = 49$, $p < 0.001$ and $F = 29.19$, $df = 1$, $p < 0.001$) (Fig. 5). The data from the experiments with oxytocin receptor antagonist were analyzed as described by Arunlakshana and Schild (19). The antagonist yielded straight line ($y = -0.51x + 4.21$; $r = 0.901$) with slope of 0.51, and pA_2 value of 8.17 ± 3.93 (SEM = 1.7; $n = 3$) (Fig. 6). The 95% confidence limits were -3.66 (lower) and 2.63 (upper) for slope, and -19.9 (lower) and 28.4 (upper) for y-intercept. Since the slope was far from the accepted value for competitive antagonists (0.9 to 1.1), the pA_2 value of 7.94 ± 0.67 ($n = 4$) was calculated from constrained Schild's plot.

Discussion

Due to the structural similarity between oxytocin and vasopressin, the two hormones can activate not only their own but also each other's receptors: in higher concentrations, vasopressin activates oxytocin receptors (22) and oxytocin activates vasopressin V_1 receptors (23). To differentiate whether the activation of oxytocin or vasopressin receptors underlies relaxant effect of oxytocin, we have used selective antagonists of V_1 receptors [(β-mercapto-β,β-cyclopentaethylene-propionyl1,0-me-tyr2,arg8)-vasopressin)], V_2 receptors ([1-(β-mercapto-β,β-cyclopentamethylene-propionic acid), 2-D-isoleucine, 4-D-isoleucine]arginine- vasopressin, and oxytocin receptors [(Deamino-Cys^1,D-Tyr (Et)^2, Thr^4, Orn^8)-oxytocin]. Whereas V_1 and V_2 antagonists used in our study have appreciable degree of selectivity (24-28), the antagonist selective only for oxytocin receptors was not available (29). [Deamino-Cys^1,D-Tyr (Et)^2, Thr^4, Orn^8]-oxytocin blocks primarily oxytocin receptors, but in higher concentrations binds to V_1 receptors, too (29-33).

Since our patients had had irregular uterine bleeding for a few months before surgery, it was not possible to determine the phase of menstrual cycle at the time of operation. However, since uterine fibroids are accompanied by hyperestrinism (3,34), and estrogen increases the expression of oxytocin receptors in oviduct (10), we could expect reasonable sensitivity of our isolated preparations to oxytocin. Besides, in our previous study (2) we have shown that the phase of menstrual cycle did not affect sensitivity of isolated human oviduct to oxytocin.

Both V_1 and V_2 antagonists in this study did not affect the relaxant effect of oxytocin on isolated isthmus and ampullas. The maximum concentrations used were about 10 times higher than concentrations necessary for effective V_1 or V_2 receptor blockade (10 nmol/L) (24-28). On the other hand, [Deamino-Cys^1,D-Tyr (Et)^2, Thr^4, Orn^8]-oxytocin was a potent blocker of isolated ampulla and isthmus relaxations caused by oxytocin. These results suggest that the oxytocin effect was probably mediated through oxytocin rather than vasopressin receptors, since the pA_2 values for the oxytocin antagonist used in our study that were obtained by Schild's plot were about 8.0 in both the isthmus and the ampulla. This corresponded to the blocking effect of the same antagonist observed in a study on isolated myometrial cells expressing oxytocin receptors (35). In another study of the same oxytocin antagonist on tissue expressing V_1 receptors, the pA_2 values obtained were significantly higher, about 9.0 (23). However, since action of [Deamino-Cys^1,D-Tyr (Et)^2, Thr^4, Orn^8]-oxytocin was non-competitive in its nature, we can not conclude that oxytocin acted via a homogenous population of oxytocin receptors.

This relaxing effect of oxytocin could be important for transportation of ova to the uterine tubes, since intermittent contractions and relaxations of the ampulla are necessary for the production of negative intraluminal pressure (36). Stimulation of sensory receptors in walls of vagina and uterine cervix during coitus causes release of oxytocin and vasopressin from the neurohypophysis (37). If coitus occurrs during the periovulatory phase, the relaxation caused by oxytocin could help create negative intraluminal pressure in the ampulla, thus sucking the ovum from the peritoneal cavity into the uterine tube, where it is retained until fertilization. Therefore, oxytocin could become an important drug in treatment of women with tubal disorders.

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