Potentiation of Uterine Effects of Prostaglandin $F_{2\alpha}$ by Adenosine 5′-Triphosphate

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OBJECTIVE: To investigate the interaction of exogenous adenosine 5′-triphosphate (ATP), a P2 receptor agonist, with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) on pregnant women in labor as well as on isolated human pregnant uterus preparations.

METHODS: For an in vitro study, myometrial samples were obtained from 27 women undergoing elective cesarean delivery at term. Concentration-response relationships for ATP (10^{-8} –3×10^{-4} mol/L), $PGF_{2\alpha}$ (10^{-9} –10^{-5} mol/L), and their combination were obtained by using routine pharmacological organ bath technique. An in vivo study was performed with 34 pregnant women with dysfunctional abnormalities of the active stage of labor who were randomly allocated into 2 study groups. The women in the control group (18 patients) received intravenous prostaglandin $F_{2\alpha}$ at an initial rate of 7.5 μg/min, whereas the women in the ATP group (16 patients) received prostaglandin $F_{2\alpha}$ concomitantly with ATP (0.45 nmol/min, intravenously).

RESULTS: Adenosine 5′-triphosphate at concentrations of 10^{-6} –3×10^{-4} mol/L and $PGF_{2\alpha}$ at concentrations of 10^{-8} –10^{-5} mol/L caused concentration-dependent contractions of isolated smooth muscle preparations of the human pregnant uterus. At concentrations of 10^{-6} mol/L and below, ATP had no effects on mechanical activity of the isolated uterus, but at concentrations of 10^{-7} mol/L and 10^{-6} mol/L, it significantly potentiated the contractile responses of the uterus induced by $PGF_{2\alpha}$ ($P < .05$, 2-way analysis of variance). Patients receiving intravenous infusion of ATP as a supplement to $PGF_{2\alpha}$ treatment, compared with those without ATP, had a significantly shorter interval from the start of the treatment to full cervical dilatation (3.31 ± 1.49 hours and 4.67 ± 1.11 hours in ATP and control groups, respectively; $P = .014$, Wilcoxon Mann-Whitney test). The total dose of prostaglandin received was significantly lower in the ATP group than that of controls (1,489.8 ± 699.9 μg and 3,394.2 ± 1,951.9 μg, respectively; $P = .003$, Wilcoxon Mann-Whitney test). No side effects of ATP treatment were observed during or after infusion.

CONCLUSION: Adenosine 5′-triphosphate potentiates effects of $PGF_{2\alpha}$ on pregnant human uterus in vitro and in vivo and thus could be a useful supplemental drug to increase uterine contractility at labor. (Obstet Gynecol 2005;105: 1429–36. © 2005 by The American College of Obstetricians and Gynecologists.)

LEVEL OF EVIDENCE: I

The reported rate of abnormal labor caused by uterine dysfunction is showing a tendency to increase nowadays, making up 8–20% of all labors,[1–4] which makes it the most common indication for primary cesarean delivery.[5] Since many repeat cesareans are performed subsequent to primary operations for dystocia, approximately 50–60% of all cesarean births in the United States may be related to dystocia.[5] Dystocia brings numerous complications, both for mother and fetus, but for the last 2 decades no drugs targeting uterine activity have been developed, and all the recommendations suggest only new combinations of well-known drugs, changes in dosage, and ways of administration. Therefore, the study of new and unexplored mechanisms of uterine contractility has not only theoretical, but also practical meaning for the development of new pharmacological drugs to correct abnormal labor.

It is now widely accepted that adenosine 5′-triphosphate (ATP), in addition to its important intracellular role as an universal source of energy, regulates many cell functions by acting on special types of receptors, called P2 receptors.[6] According to the current classification, P2 receptors are divided into 2 families: P2X and P2Y receptors, with P2X receptors being ligand-gated ion channels, while P2Y receptors are G-protein-coupled.[6,7] In smooth muscles, stimulation of P2X receptors causes contractile responses, whereas stimulation of P2Y receptors usually leads to relaxant effects.[8]

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The presence of P2 receptors has been shown in many animal and human tissues, including those of reproductive system.[6] P2 receptor-mediated responses have been described in the isolated nonpregnant uterus of rats, mice, guinea pigs, and rabbits, as well as in pregnant uterus of rats and rabbits.[9–16] However, until our recent publications,[17,18] evidence for the presence of functionally active P2 receptors in the human uterus was absent. We have shown that, in the isolated smooth muscle preparations taken from human pregnant uterus, P2 receptor agonists evoke contractile responses that are significantly inhibited by the P2 receptor antagonist, pyridoxalphosphate-6-azophenyl-2′,4′-disulphonic acid (PPADS).[17] Furthermore, we found that indomethacin, an inhibitor of prostaglandin synthesis, reduced, whereas $\mathcal{N}^{G}$-nitro-L-arginine methyl ester (L-NAME), an inhibitor of nitric oxide synthase, enhanced contractile responses of the uterus caused by ATP, suggesting the involvement of prostaglandins and nitric oxide (NO) in the ATP-induced responses.[18]

We found an early report showing that an intramuscular injection of ATP given to pregnant women during labor increases uterine contractility.[19] This finding, however, has been neglected by clinicians and scientists, and neither the author herself nor anyone else extended that study.

The aim of the present study was to investigate the interaction of ATP with prostaglandin $F_{2\alpha}$, the drug that is commonly used in Russia to increase uterine contractility during labor.[20–22] To test the hypothesis that intravenous administration of ATP to women with dysfunctional labor would augment the stimulant effects of the prostaglandin $F_{2\alpha}$ on uterine activity and increase the rate of cervical ripening and dilation, we carried out a single-blind randomized trial on women suffering dysfunctional labor who were being treated with prostaglandin $F_{2\alpha}$.

MATERIALS AND METHODS

The study was approved by the Ethical Committee of Kazan State Medical University, and documented, informed consent was obtained from each woman who took part in the study.

Full-thickness myometrial samples were obtained from the superior edge of a transverse uterine incision from 27 women undergoing elective cesarean delivery at term. The tissue samples were placed immediately in the precooled modified Krebs solution and used within 2–4 hours for pharmacological organ bath studies. The Krebs solution was of the following composition (mmol/L): NaCl 133, KCl 4.7, $NaHCO_3$ 16.4, $MgSO_4$ 0.6, NaH_2PO_4 0.8, $CaCl_2$ 2.5, and glucose 7.7, and was gassed continuously with 95% O_2 and 5% CO_2, (pH 7.3–7.4). Strips of smooth muscle, approximately 2×10 mm, were prepared without the endometrium. The preparations were suspended vertically in 10-mL tissue baths for isometric recording of mechanical activity; the bath temperature was kept 37 ± 0.5°C by a TE-8A water pump (Techne, Cambridge, UK). Mechanical activity of the tissues was recorded isometrically with a FSG-01 force-displacement transducer (Linton Instrumentation, Norfolk, UK), data were recorded and stored digitally by a BIOPACK (BIOPACK Systems Inc, Santa Barbara, CA) MP100WSW data acquisition system, and displayed on a computer screen.

Concentration-response curves for prostaglandin $F_{2\alpha}$ (10^{-8}, 10^{-7}, 10^{-6}, and 10^{-5} mol/L; Enzaprost F, Gedeon Richter, Budapest, Hungary) and ATP (10^{-6}, 10^{-5}, 10^{-4} and $3*10^{-4}$ M, adenosine 5′-triphosphate sodium salt; Sigma, Gillingham, UK) were obtained by adding the agent directly to the organ bath, and the tissue was washed with a fresh Krebs solution after a maximum amplitude of contraction (peak or plateau) or null-response (within 2–3 minutes) had been observed. Intervals of 10 minutes were allowed between additions of successive concentrations of the agonists.

In a different set of experiments, after an initial concentration-response relationship for prostaglandin $F_{2\alpha}$ had been obtained, the second and third concentration-response curves for prostaglandin $F_{2\alpha}$ were constructed in the presence of a given concentration of ATP (10^{-8}, 10^{-7}, 10^{-6}, or 10^{-5} mol/L), which was added to the organ bath 20 seconds before addition of each concentration of prostaglandin $F_{2\alpha}$. Typically, only 2 of the 4 above-mentioned concentrations of ATP were tested on the same tissue preparation.

In the experiments with PPADS (pyridoxalphosphate-6-azophenyl-2′,4′-disulphonic acid; Tocris, Bristol, UK), after an initial concentration-response relationship for prostaglandin $F_{2\alpha}$ had been obtained, a second relationship was established in the presence of ATP at a concentration of 10^{-7} or 10^{-6} mol/L, and a third concentration-response curve was constructed in the presence of the same concentration of ATP after incubation of the tissues with PPADS (10^{-5} mol/L) for at least 30 minutes. All contractile responses were expressed as a percentage of the contractions evoked by 240 mmol/L potassium chloride (KCl), which was applied at the very end of the experiment.

The study of the possible positive effects of ATP in the management of dysfunctional labor was carried out in the obstetrics clinic of Republic Hospital No. 3 (Kazan, Russia) over a period of 3 months from February 1, 2004, to April 30, 2004, with permission from the Ethical Committee. All patients scheduled for induction and

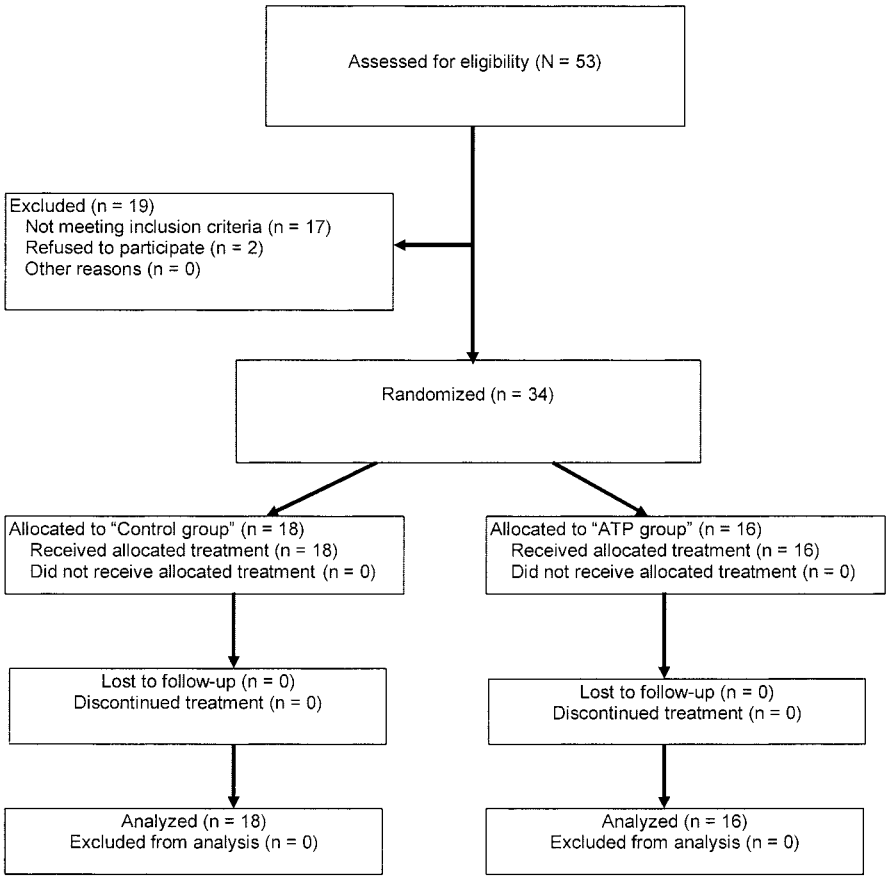

Fig. 1. Flow diagram of the progress of subjects through the phases of the randomized trial. ATP, adenosine 5′-triphosphate.

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augmentation of labor in the obstetrics clinic were evaluated for possible inclusion in the study. During the study period, 53 parturients underwent augmentation of labor, and 34 (64%) of them were recruited for the study (Fig. 1).

Patient inclusion criteria were as follows: parturients with hypotonic uterine dysfunction, term pregnancies (37–41 weeks), and ruptured membranes, either spontaneously or artificially. The diagnosis was based on infrequent, low-intensity contractions (less than 30 mm Hg and frequency less than 2 per 10 minutes, ie, less than 60 Montevideo units) and the absence of cervical response to labor. Exclusion criteria were as follows: nonvertex presentation, multifetal gestation, previous uterine surgery, preterm delivery (before 37 weeks), any contraindication to vaginal delivery (placenta previa), chronic hypertension, diabetes mellitus, and hypersensitivity to prostaglandins or ATP.

After applying the exclusion criteria, patients were assigned to the treatment groups according to the computer-generated randomized schedule provided by the hospital. The patients were blinded to the received treatment; the staff were not blinded. All patients were managed by resident physicians under the supervision of faculty members.

After recruitment, baseline data, such as maternal age, gestational age, complications of pregnancy, and initial Bishop score, were collected. Uterine activity and fetal heart rate (FHR) were also monitored by an external detector (Fetalgard 3000; Analogic Corporation, Peabody, MA). Bradycardia (FHR less than 100 beats per minute for longer than 2 minutes) and repetitive or severe variable decelerations were defined as a nonreassuring fetal status.

The women of control group (18 patients) received prostaglandin $F_{2\alpha}$ (Enzaprost F, 1-mL ampoule of 5 mg/mL solution, Gedeon Richter) by continuous intravenous drip-infusion, whereas the women of ATP group (16 patients) received the same dose of prostaglandin $F_{2\alpha}$ concomitantly with ATP (adenosine triphosphate sodium salt, 1-mL ampoule of 1% solution, Biomed, Perm, Russia) administered through a contralateral vein by continuous drip-infusion. The initial rate of prostaglandin $F_{2\alpha}$ infusion in both groups was 7.5 μg/min (20 nmol/min), and this was increased if the patient was not responding, whereas the rate of ATP infusion was 0.25

μg/min (0.45 nmol/min) and was fixed during the whole procedure. After the beginning of infusion, the patient's blood pressure and pulse were checked every hour. Patients not responding to the therapy, ie, without cervical dilation within 2 hours of infusion, were delivered by cesarean.

The primary outcome measure was the interval from the start of the induction and full cervical dilatation (ie, the beginning of the second stage of labor). Secondary outcome variables included the interval from the start of the induction and the increase in the uterine contractility, total dose of prostaglandin $F_{2\alpha}$ injected, the route of delivery, the indications for operative delivery, and indications of fetal compromise, such as low Apgar score and admission to the neonatal intensive care unit.

For evaluation of concentration-effect relationships in vitro, experimental curves were fitted to a nonlinear regression analysis. Differences between mean values of groups with normally distributed variables were assessed using Student paired *t* test, as well as by 2-way analysis of variance (ANOVA). To evaluate normality of variances, Kolmogorov-Smirnov and Shapiro-Wilk normality tests were used, and homogeneity of variances was estimated using Levene and Brown-Forsythe tests. Differences between continuous variables that were not normally distributed were evaluated by Wilcoxon signed rank test (in vitro) and Wilcoxon Mann-Whitney test (in vivo). Differences in Bishop score were evaluated by Kruskal-Wallis test. Differences in discontinuous variables, such as mode of delivery and the number of complications, were analyzed with χ^2 or Fisher exact tests, when appropriate. A probability value of less than or equal to .05 was considered significant.

The statistical analyses of in vitro data were carried out by using GraphPad (San Diego, CA) Prism 4.00 software. Analyses of clinical data were performed by using SPSS 11.0 (SPSS Inc, Chicago, IL). Data are presented as mean ± standard error of the mean (in vitro data) and as mean ± standard deviation (in vivo data).

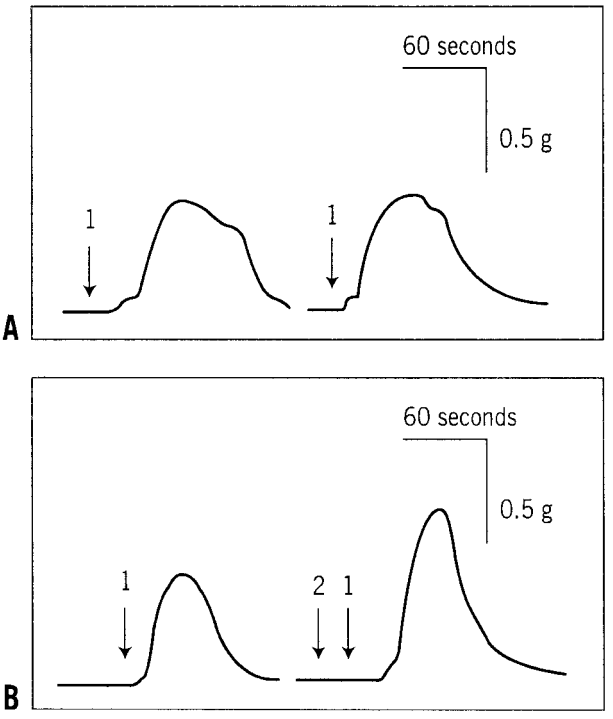

Fig. 2. A. Original traces of a time-control experiment. A given tissue was challenged by prostaglandin $F_{2\alpha}$ at concentrations of 10^{-8}, 10^{-7}, 10^{-6}, and 10^{-5} mol/L 3 consecutive times. Traces shown are the first and the third contractions evoked by prostaglandin $F_{2\alpha}$ at a concentration of 10^{-7} mol/L. *Arrows* indicate the moment of introduction of prostaglandin $F_{2\alpha}$. **B.** Original traces of contractions of isolated strips of human pregnant uterus evoked by prostaglandin $F_{2\alpha}$ at a concentration of 10^{-7} mol/L in the absence (left) and presence (right) of adenosine 5′-triphosphate (ATP) at a concentration of 10^{-6} mol/L. *Arrows* indicate the moment of introduction of drugs: 1, prostaglandin $F_{2\alpha}$; 2, ATP.

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RESULTS

In preliminary experiments, we found that uterine contractility did not significantly change in time. Repeated concentration-response curves for prostaglandin $F_{2\alpha}$ and ATP were statistically identical (2-way ANOVA, $P > .05$; Fig. 2A).

Prostaglandin $F_{2\alpha}$ (10^{-8} –10^{-5} mol/L) and ATP (10^{-6} –3×10^{-4} mol/L) both caused concentration-dependent contractions of the isolated pregnant uterus preparations. Contractile responses of the preparations to prostaglandin $F_{2\alpha}$ were usually in a style of all-or-nothing, giving a steep concentration-effect curve in the individual tissues. Responses of the uterus to ATP usually gave a less steep curve (Fig. 3).

Adenosine 5′-triphosphate at concentrations of 10^{-6} mol/L and below had no effect on contractility of myometrium preparations. However, the addition of ATP at concentrations of 10^{-7} or 10^{-6} mol/L, 20 seconds before the addition of each single concentration of prostaglandin $F_{2\alpha}$, significantly enhanced the amplitude of the contractions caused by this uterotonic agent (Fig. 2B). At concentrations of 10^{-8} mol/L and 10^{-5} mol/L, ATP had no influence on prostaglandin $F_{2\alpha}$-induced contractions of the uterus (Fig. 4).

Incubation of the tissues with PPADS (10^{-5} mol/L) did not significantly alter the contractile effects of

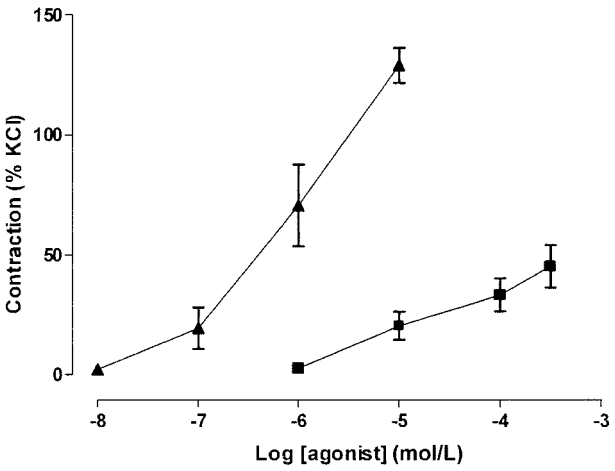

Fig. 3. Contractions of isolated myometrial preparations from human pregnant uterus evoked by adenosine 5′-triphosphate (ATP) (*squares*, n = 17) and prostaglandin $F_{2\alpha}$ (*triangles*, n = 13). Data are shown as a percentage of the response of the tissue to potassium chloride (KCl, 240 mmol/L). Vertical bars represent standard error of the mean.

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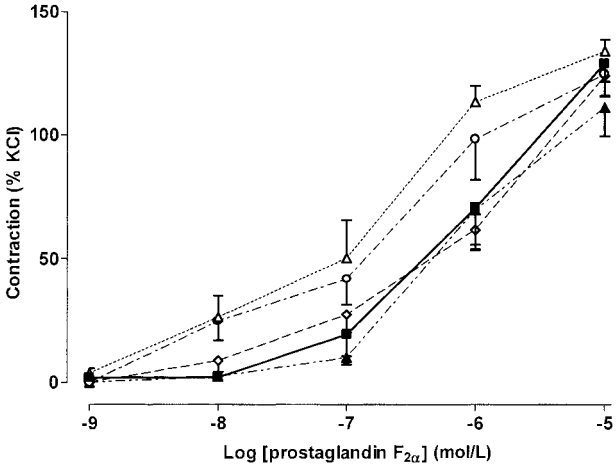

Fig. 4. Contractions of the isolated human pregnant uterus caused by prostaglandin $F_{2\alpha}$ (controls, *closed squares*) in the presence of adenosine 5′-triphosphate (ATP) at concentrations of 10^{-8} mol/L (*closed triangles*), 10^{-7} mol/L (*open triangles*), 10^{-6} mol/L (*circles*), and 10^{-5} mol/L (*rhombs*). Data are shown as a percentage of the response of the tissue to potassium chloride (KCl, 240 mmol/L). Vertical bars represent standard error of the mean, n = 9–17. Note that concentration-response curves for prostaglandin $F_{2\alpha}$ in the presence of ATP at concentrations of 10^{-7} and 10^{-6} mol/L are significantly different from the control curve ($P < .05$, 2-way analysis of variance test).

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prostaglandin $F_{2\alpha}$ on the myometrium. Pyridoxalphosphate-6-azophenyl-2′,4′-disulphonic acid abolished the ATP-induced enhancement of prostaglandin-evoked contractions when ATP was used at a concentration of 10^{-6} mol/L (Fig. 5A). However, PPADS did not affect the ATP-induced potentiation of prostaglandin-evoked contractions when ATP was used at a concentration of 10^{-7} mol/L (Fig. 5B).

There were 2 multigravidas and 14 nulliparas in the ATP group and 4 multigravidas and 14 nulliparas in the control group. The mean age was 26.2 ± 6.2 years in the ATP group and 25.9 ± 3.4 years in the control group, with the estimated gestation age of 40.0 ± 0.9 weeks and 39.1 ± 1.3 weeks, respectively ($P > .05$ in both cases, Wilcoxon Mann-Whitney test). The Bishop scores at the beginning of the therapy were 5.31 ± 1.45 in the ATP group and 5.28 ± 1.53 in the control group ($P > .05$, Kruskal-Wallis test).

The interval from the start of the induction and full cervical dilatation (ie, the beginning of the second stage of labor) was significantly shorter in the ATP group than in the control group (3.31 ± 1.49 hours and 4.67 ± 1.11 hours, respectively; $P = .014$, Wilcoxon Mann-Whitney test). The interval from the start of the induction and the increase in the uterine contractility was 8.8 ± 3.6 minutes in the ATP group and 16.4 ± 8.0 minutes in the control group ($P = .01$, Wilcoxon Mann-Whitney test). In the ATP group there were no indications for increasing the prostaglandin infusion rate, compared with the control group, in which 9 of the 18 patients required an increase in the rate of infusion of 2–3 times to enhance the frequency and the intensity of the uterine contractions. The total dose of prostaglandin received was 1,489.8 ± 699.9 μg in the ATP group and 3,394.2 ± 1,951.9 μg in the control group ($P = .003$, Wilcoxon Mann-Whitney test).

The mean blood loss was similar in both groups (292.0 ± 215.8 mL in the ATP group and 378.1 ± 216.3 mL in the control group; $P > .05$, Wilcoxon Mann-Whitney test). No cases of uterine hyperstimulation were registered in either group, but cervical laceration was registered in 4 patients in the ATP group and in 7 patients in the control group.

The duration of the second period of labor was 25.7 ± 6.5 minutes and 26.1 ± 10.4 minutes, and the total duration of labor was 8.49 ± 2.87 hours and 8.64 ± 2.64 hours in the ATP and control groups, respectively ($P > .05$ in both cases, Wilcoxon Mann-Whitney test).

Two patients in the ATP group were delivered by cesarean because acute nonreassuring fetal status was diagnosed. In the control group, 4 women were deliv-

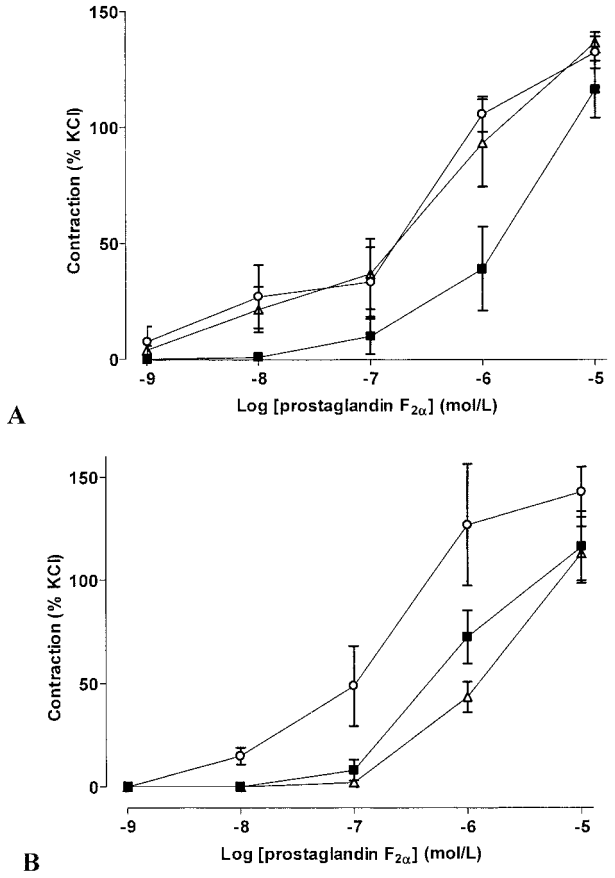

Fig. 5. Effects of pyridoxalphosphate-6-azophenyl-2′,4′-disulphonic acid (PPADS) (10^{-5} mol/L, *triangles*) on the contractions of the isolated human pregnant uterus caused by prostaglandin $F_{2\alpha}$ (controls, *squares*) in the presence of adenosine 5′-triphosphate (ATP, *circles*) at a concentration of 10^{-7} mol/L **(A)** and 10^{-6} mol/L **(B)**. Data are shown as a percentage of the response of the tissue to potassium chloride (KCl, 240 mmol/L). Vertical bars represent standard error of the mean, n = 6–14. Note that, in panel **A**, concentration-response curves for prostaglandin $F_{2\alpha}$ in the presence of ATP (with and without PPADS) are significantly different from the control curve ($P < .05$, 2-way analysis of variance test). In panel **B**, concentration-response curve for prostaglandin $F_{2\alpha}$ in the presence of ATP without PPADS is significantly different from the control curve ($P < .05$, 2-way analysis of variance test), while that with PPADS is not.

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ered by cesarean where the indications were protracted active phase dilation (2 patients), secondary arrest of dilation (1), and acute nonreassuring fetal status (1). Calculation of number needed to treat to prevent delivery by cesarean gave 10 patients. On the other hand, number need to harm (to cause nonreassuring fetal status) was calculated as 14 patients.

There were no differences between the 2 groups in terms of neonate condition: Apgar scores at the fifth minute were 7.25 ± 0.45 in the ATP group and 7.44 ± 0.51 in the control group ($P > .05$, Wilcoxon Mann-Whitney test). In neither group was the Apgar score at the fifth minute lower than 7. The neonatal outcomes in both groups were comparable. There was no intergroup difference in the number of admissions to the special care neonatal unit or in the duration of hospital stay. No infant required intubation or prolonged resuscitation. Cases of postpartum complications and maternal morbidity were also similar in both groups. There were no significant changes in either blood pressure or cardiac rhythm of patients during ATP infusion; none of the patients complained about pain in the arm or hand in which ATP was being infused. In the postpartum period, there were no signs of inflammation in or around the ATP-infused vein.

DISCUSSION

In this study we have shown that in the human pregnant uterus ATP, besides its own contractile activity, can potentiate prostaglandin $F_{2\alpha}$-evoked contractions. We suggest that P2 receptors may play a physiological role because they are involved in the regulation of the contractility of the uterus during labor. Moreover, in our preliminary clinical study, we have found that ATP could be a useful additional tool to increase uterine contractility during childbirth.

Earlier, we showed that P2 receptor agonists caused concentration-dependant contractions of human pregnant uterus with the rank order of potency of α, β-methylene-ATP > uridine 5′-triphosphate (UTP) > ATP = adenosine 5′-diphosphate (ADP).[17] Although this rank order of potency is not entirely consistent with those for any individual subtype of P2 receptors described,[23] we suggested the presence of P2X receptor in human pregnant uterus because the most active agonist was α, β-methylene-ATP,[17] which is known to be a potent $P2X_1$ and $P2X_3$ receptor agonist.[23,24] That suggestion was also supported by the antagonistic effectiveness of PPADS,[17] a relatively selective P2X receptor antagonist in organ-bath experiments.[25,26] However, because of the relatively high potency of UTP in this tissue, we could not discard the possibility of a $P2Y_2$ or $P2Y_4$ receptor being involved.

The results from the organ-bath studies presented in this paper show that concentrations of ATP, which itself did not evoke mechanical activity in isolated preparations of myometrium from pregnant women, markedly

potentiate the contractile action of prostaglandin $F_{2\alpha}$. This effect of ATP was concentration-dependent, being evident at over a range of 2 orders of magnitude, but being absent at both low (10^{-8} mol/L) and high (10^{-5} mol/L) concentrations. Pyridoxalphosphate-6-azophenyl-2′,4′-disulphonic acid did not affect the potentiating effects of 10^{-7} mol/L ATP, but it abolished, or even converted to an inhibition, the potentiating effects of 10^{-6} mol/L ATP. This implies that these 2 concentrations of ATP are acting via different populations of receptors. Because PPADS blocks the direct contractile effects of 10^{-4} mol/L ATP in this tissue,[17] and because the higher concentration, not the lower concentration of ATP, was blocked, it is unlikely that PPADS is providing a surmountable antagonism. Thus, the spectrum of P2 receptors involved in response to P2 agonists and in ATP-induced potentiation of prostaglandin-evoked contractions in isolated human pregnant uterus is yet to be investigated.

Intravenous administration of ATP to women with dysfunctional labor augmented the stimulant effects of the prostaglandin $F_{2\alpha}$ on uterine activity. It also increased the rate of cervical ripening and dilation, reduced the total dose of prostaglandin received, and reduced the risk of cesarean delivery. These results show that the potentiating effects of ATP on prostaglandin $F_{2\alpha}$ activity in the uterus translate well from the organ-bath to the person. Women with dysfunctional labor significantly benefited from the combination treatment of Enzaprost F plus ATP, compared with women given Enzaprost F alone.

It is important to note that ATP did not cause any detectable adverse effects, which we would expect from its pharmacological profile.[27] There was no significant change of arterial blood pressure or heart rate. Also, it is known that ATP can induce pain and inflammation at the site of injection,[28,29] most likely because of activation of $P2X_3$ receptors.[30] However, none of the women complained about pain in the hand or along the vein where ATP was infused.

Although the initiation of this clinical trial was based on the observation of clear potentiation of prostaglandin $F_{2\alpha}$-evoked contractions by ATP, and although the results in vivo complement the data obtained in vitro, the clinical trial has some limitations. The sample sizes were small, but this was limited by the period of permission for carrying out the trial (3 months) that was obtained from the local Ethical Committee. We found no significant difference in the rate of cesarean delivery between the groups, but for a 10.3% cesarean rate to be significant at a level of .05 (ie, 12.5% and 22.2%), approximately 110 persons are needed in each group. Similarly, the size of the study was not adequate to show any significant differences between groups in the rate of nonreassuring fetal status: for a 7% nonreassuring fetal status rate to be significant, approximately 150 patients are needed in each group at a significance level of .05.

Although prostaglandin $F_{2\alpha}$ has numerous adverse effects and contraindications, it is commonly used in Russian obstetrics clinics for labor augmentation, either alone or in combination with oxytocin.[20–22] As a development of this study, we are currently involved in a project designed to test interactions of ATP with oxytocin, both in vitro and in vivo.

At present, ATP is the only P2 receptor agonist used in clinical practice, apart from UTP for dry eye and cystic fibrosis.[31] Therapeutic effects of intravenous infusion of ATP have been demonstrated in the treatment of chronic obstructive pulmonary disease,[32] pulmonary hypertension,[33] supraventricular tachycardia,[34] and lung cancer,[35] and ATP has been used to induce pharmacological hypotension during surgery.[27] Results of the current study open up a possible new area for introducing P2 receptor agonists, and possibly antagonists, in clinical medicine as drugs to regulate uterine contractility during pregnancy and labor.

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