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Abstract

L-Dopa and three catecholamines in the amniotic fluid before and after labor were measured to confirm the amniotic fluid catecholamine levels at the end of gestation. L-Dopa values were higher than those of three catecholamines, and dopamine which was the predominant catecholamine, rose significantly after the onset of labor. Then, to evaluate the effects of L-dopa or dopamine on prostaglandin synthesis, strips of human decidua vera obtained from fetal membranes at the time of elective cesarean sections before the onset of labor were incubated in Krebs-Ringer buffer in the presence of L-dopa or dopamine. When L-dopa was added, the net production of prostaglandin(PG)F was significantly greater than that of the control at each incubation time. On the other hand, the significant rise was observed only after 10 min of incubation for PGE2 production. Dopamine had a stimulatory effect on PGF synthesis only after 15 and 30 min of incubation, and it also stimulated the release of PGE2 at each incubation time. These results suggest that dopamine and L-dopa in amniotic fluid stimulate the production of prostaglandin by the decidua in humans.

KEYWORDS: L-dopa, dopamine, prostaglandin, decidua vara, amniotic fluid

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Effects of L-Dopa or Dopamine on Human Decidual Prostaglandin Synthesis

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L-Dopa and three catecholamines in the amniotic fluid before and after labor were measured to confirm the amniotic fluid catecholamine levels at the end of gestation. L-Dopa values were higher than those of three catecholamines, and dopamine which was the predominant catecholamine, rose significantly after the onset of labor. Then, to evaluate the effects of L-dopa or dopamine on prostaglandin synthesis, strips of human decidua vera obtained from fetal membranes at the time of elective cesarean sections before the onset of labor were incubated in Krebs-Ringer buffer in the presence of L-dopa or dopamine. When L-dopa was added, the net production of prostaglandin(PG)F was significantly greater than that of the control at each incubation time. On the other hand, the significant rise was observed only after 10 min of incubation for PGE_2 production. Dopamine had a stimulatory effect on PGF synthesis only after 15 and 30 min of incubation, and it also stimulated the release of PGE_2 at each incubation time. These results suggest that dopamine and L-dopa in amniotic fluid stimulate the production of prostaglandin by the decidua in humans.

Key words : **L-dopa, dopamine, prostaglandin, decidua vera, amniotic fluid**

Dopamine occurs in higher concentration in human amniotic fluid than norepinephrine and epinephrine, both at midpregnancy and at term (1, 2). Furthermore, the level of dopamine in amniotic fluid is found to rise sharply near term (2, 3), however, the physiological causes and effects of increasing dopamine in amniotic fluid are unclear.

At the present time, prostaglandin(PG)E_2 and $PGF_2\alpha$, which are mainly produced by fetal membranes, are believed to have important roles in human parturition (4, 5). It was demonstrated that catecholamines, including dopamine, had a stimulatory effect on prostaglandin production *in vitro* studies (6-8), and that dopamine increased uterine contractility in women at term (9). These findings support the hypothesis that dopamine found in increasing amount in amniotic fluid during late gestation might relate to human parturition (2, 10), because amniotic fluid is in direct contact with fetal membranes. However, there is no report that dopamine accelerates prostaglandin synthesis by human fetal membranes *in vitro*.

The present study was designed to confirm dopamine levels in amniotic fluid, and to evaluate the effect of dopamine and L-dopa on prostaglandin production *in vitro* using human decidua vera from fetal membranes. As a result, we found

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that both dopamine and L-dopa stimulated prostaglandin synthesis in decidual tissue.

Materials and Methods

Subjects. Amniotic fluid was obtained from 35 term normal vaginal deliveries (VD group) and 6 term elective cesarean sections before the onset of labor (CS group). The evaluation of gestational age was based on the last menstrual period and/or on ultrasonographic examination. Spinal anesthesia was provided for the cesarean sections. Gestations were without medical complications, and all babies were delivered as appropriate for date with normal Apgar scores above 8.

Amniotic fluid samples in the VD group were obtained after the baby was born, and samples in the CS group were obtained by artificial rupture of membranes.

For the catecholamine assay, amniotic fluid samples were collected into ice cold tubes as previously described (11).

Fetal membranes for the incubation experiments were obtained from 7 term elective cesarean sections performed on women not in labor. The tissues were rinsed several times with an ice-cold solution of 0.15 M NaCl to remove clotted blood, and were immediately frozen at −80 °C until the incubation experiments.

For the incubation procedure, the specimen was immersed in Krebs-Ringer buffer, and the decidua vera was then gently separated with fine forceps. Histologic examination confirmed that this tissue was predominantly composed of decidual cells. The decidua was excised into a disc of 4.0 g wet weight.

These decidual strips were incubated in 100 ml flasks containing 50 ml of Krebs-Ringer buffer to which L-dopa or dopamine was added in a concentration of 20 ng/ml or 30 ng/ml, respectively. One hundred microliters of 5 M N-methyl-N-propargylbenzylamine(pargyline), which inhibits the activity of monoamine oxidase (MAO), was also added to the medium (final concentration 10 mM). The incubation experiments were performed at 37 °C under an atmosphere of 95 % O_2 and 5 % CO_2 for 30 min.

The concentrations of L-dopa or dopamine added to the Krebs-Ringer buffer solution were adjusted to concentrations approximately ten times greater than those in human amniotic fluid before the onset of labor. Because there is a large amount of MAO in human decidua (11), pargyline was added to the medium to inhibit the metabolism of dopamine into 3, 4-dihydroxyphenylacetic acid by MAO.

Aliquots of 1.5 ml were removed from the medium at zero time and after 5, 10, 15 and 30 min of incubation to calculate prostaglandin production per gram wet weight of tissue. The control incubations were performed without the addition of L-dopa or dopamine. The decidual strips in the control incubation were obtained from the same fetal membranes used in the L-dopa or dopamine-added experiments. All samples were frozen and stored at −40 °C until assay.

Catecholamine assay. L-Dopa and three catecholamines in the amniotic fluid, and L-dopa or dopamine in the incubation medium were assayed by high performance liquid chromatography with electrochemical detection, as previously described (11).

Prostaglandin assay. We made a slight modification of the method of Jaffe *et al.* (12) for extraction and separation of prostaglandins. The specimen was defatted with n-hexane instead of petroleum ether, and we utilized the mixture of ethyl acetate, isopropanol and water (7:3:6, v/v/v) for prostaglandins extraction. The extract was then applied to the column packed with silicic acid to separate prostaglandins. The chromatographic solvent consisted of benzene, ethyl acetate and methanol in variable ratios (60:40:X). X was 0 for solvent A, 2 for B, 6.5 for C, 12 for D, 20 for E and 30 for F.

In this study, $PGF_2\alpha$ was measured by [^{3}H] $PGF_2\alpha$ Radioimmunoassay Kit (Baxter Travenol Diagnostics, Inc., Cambridge, MA, USA), and the percentage cross reactivity was 28.2 % for $PGF_1\alpha$. The results were therefore expressed as PGF. Assay of PGE_2 was performed with the use of [^{125}I] PGE_2 Radioimmunoassay Kit (New England Nuclear Corp., Boston, MA, USA).

All data are expressed as mean ± standard error. Statistical differences were assessed by Student's *t*-test.

Results

Concentrations of L-dopa and three catecholamines in the amniotic fluid. The mean value of L-dopa and three catecholamines in the amniotic fluid is shown in Fig. 1. The concentration of L-dopa was highest in each group, and dopamine showed the highest value of the three catecholamines. Moreover, the dopamine concen-

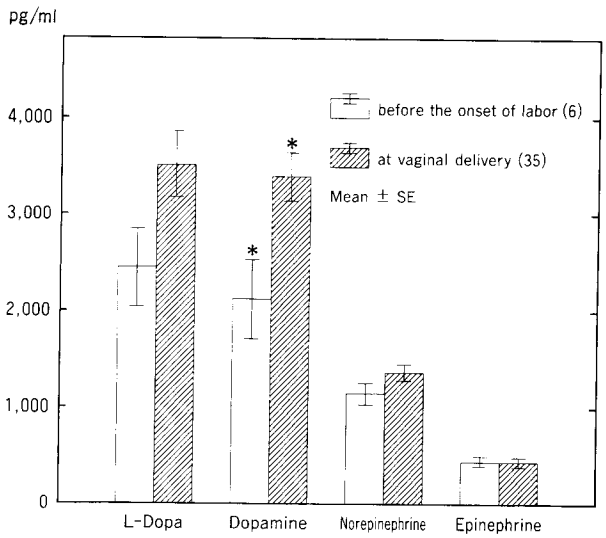

Fig. 1 The concentrations of L-dopa and three catecholamines in the amniotic fluid before the onset of labor and at vaginal delivery. Before labor, the mean value of each compound was; L-dopa: 2440.7 ± 407.4 pg/ml, dopamine: 2123.0 ± 416.5 pg/ml, norepinephrine: 1146.3 ± 112.4 pg/ml, and epinephrine: 452.8 ± 35.8 pg/ml. At delivery, that was; L-dopa: 3523.7 ± 346.7 pg/ml, dopamine: 3403.1 ± 257.1 pg/ml, norepinephrine: 1367.7 ± 75.6 pg/ml and epinephrine: 461.2 ± 24.3 pg/ml. The numbers of subjects are shown in parentheses. * $p < 0.05$

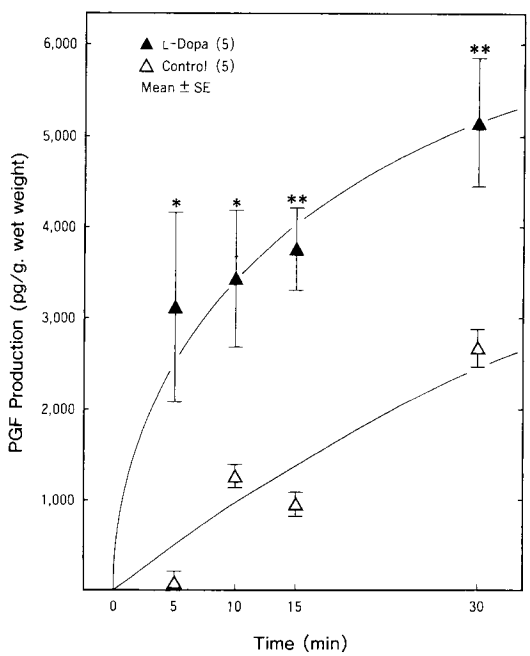

Fig. 2 Time course of PGF production by human decidual tissue in the presence of 20 ng/ml of L-dopa (closed triangles) and in the absence of L-dopa (open triangles). The numbers of incubation experiments are shown in parentheses. * $p < 0.05$, ** $p < 0.01$ compared with the control.

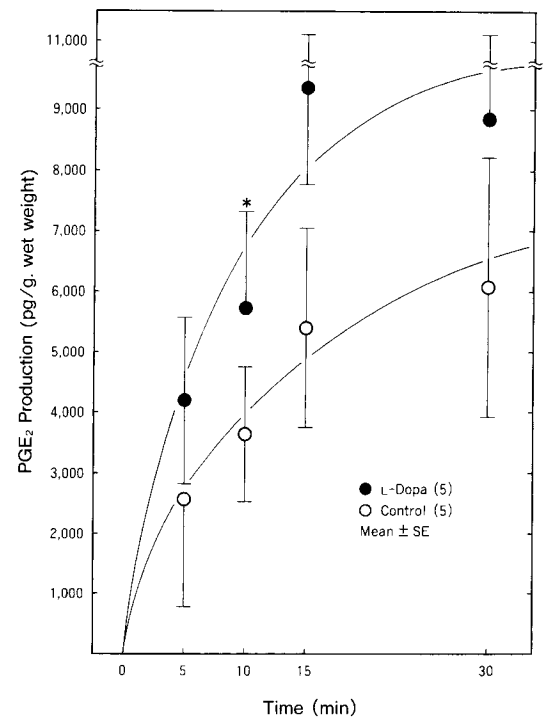

Fig. 3 Time course of PGE_2 production by human decidual tissue in the presence of 20 ng/ml of L-dopa (closed circles) and in the absence of L-dopa (open circles). The numbers of incubation experiments are shown in parentheses. * $p < 0.05$ compared with the control.

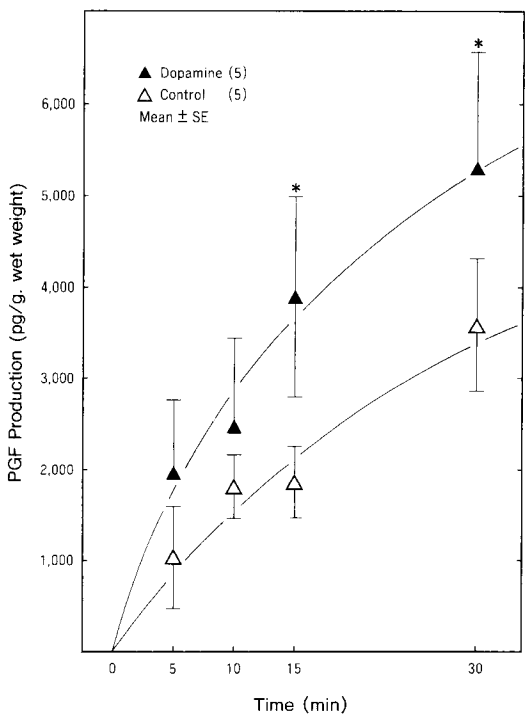

Fig. 4 Time course of PGF production by human decidual tissue in the presence of 30 ng/ml of dopamine (closed triangles) and in the absence of dopamine (open triangles). The numbers of incubation experiments are shown in parentheses. * $p < 0.05$ compared with the control.

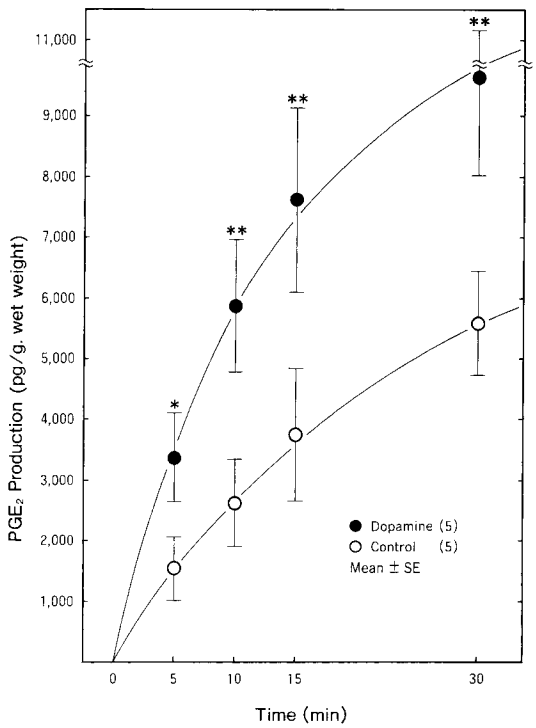

Fig. 5 Time course of PGE_2 production by human decidual tissue in the presence of 30 ng/ml of dopamine (closed circles) and in the absence of dopamine (open circles). The numbers of incubation experiments are shown in parentheses. * $p < 0.05$, * * $p < 0.01$ compared with the control.

tration after labor commenced was significantly ($p < 0.05$) higher than before labor commenced.

The effect of L-dopa on decidual prostaglandin synthesis. When L-dopa was added to the medium ($n = 5$), L-dopa significantly stimulated the PGF production at each incubation time (Fig. 2). PGE_2 production at each incubation time was higher than the control. However, the significant rise of PGE_2 production was observed only after 10 min of incubation (Fig. 3).

The effect of dopamine on decidual prostaglandin synthesis. When dopamine was added to the medium ($n = 5$), dopamine had a stimulatory effect on PGF production after 15 and 30 min of incubation (Fig. 4). The release of PGE_2 was significantly higher than the control at each incubation time (Fig. 5).

The concentrations of L-dopa or dopamine in the medium. The concentrations of L-dopa and dopamine were measured at each incubation time to cofirm whether added L-dopa or dopamine was converted to another compound.

The mean concentrations of L-dopa and dopamine at zero time were about half of the initial concentrations, and there was almost no change of L-dopa and dopamine concentrations with the progression of incubation time. L-Dopa and dopamine were the only catecholamines detected in the medium.

Discussion

It is well known that catecholamine concentrations in amniotic fluid increase with the progression of pregnancy, and dopamine concentration increases markedly at the end of gestation compared with norepinephrine and epinephrine (2, 3). We showed the predominance of dopamine and L-dopa in amniotic fluid at term. Furthermore, we determined that the amniotic fluid dopamine level in this study increased significantly after the onset of labor. Ben-Jonathan and Munsick (1) indicated that dopamine in human amniotic fluid is biologically active, as judged by its ability to inhibit rat pituitary prolactin secretion. However, the physiological role of the increasing quantity of amniotic fluid dopamine near term remains unknown.

It is well established that PGE_2 and $PGF_2\alpha$, mainly produced by fetal membranes, are present at high levels in human amniotic fluid. PGE_2 and $PGF_2\alpha$ produced by fetal membranes are believed to be actively involved in the initiation and/or maintenance of human parturition (4,5). Some authors reported that catecholamines, including dopamine, stimulated prostaglandin synthesis *in vitro* experiments (6–8), and that dopamine infusion induced uterine contractions in humans (9) and animals (13). From these observations, Phillippe and Ryan (2, 10) speculated that increasing amniotic fluid dopamine is concerned with human parturition through prostaglandin production by fetal membranes.

In addition to dopamine, we paid attention to L-dopa, a precursor of dopamine, which was predominant in amniotic fluid. Thereafter, we studied whether L-dopa or dopamine contributes to decidual prostaglandin synthesis *in vitro*. Fetal membranes consist of amnion, chorion and decidua vera. Prostaglandins produced in decidua vera, which is in direct contact with uterine muscle tissue, are considered to cause uterine muscle contractions (4). Therefore, we elected to use decidual tissue in this study.

Data from the incubation experiments indicated that L-dopa had a stimulatory effect on PGF production, but did not stimulate PGE_2 production after the first 10 min of incubation. The release of PGF and PGE_2 by decidual strips increased significantly compared with the control by the addition of dopamine. Catecholamines appear to activate phospholipase A_2 which converts phospholipid into arachidonic acid (7, 14, 15), or to activate prostaglandin synthetase which converts arachidonic acid into PGE_2 and $PGF_2\alpha$ (6, 8). It has been demonstrated that these two enzymes are also present in human decidua (4, 15, 16). In this study, we first described that L-dopa, the precursor of dopamine, stimulated prostaglandin biosynthesis.

However, evidence that L-dopa directly activates phospholipase A_2 or prostaglandin synthetase is lacking. Although no catecholamine except for L-dopa was detected in the medium at any incubation time, the possibility remains that L-dopa is converted to dopamine in the decidual tissue and this dopamine activates phospholipase A_2 or prostaglandin synthetase. Further investigations into the relationship between the catecholamines, L-dopa and dopamine, and the enzymes, phospholipase A_2 and prostaglandin synthetase in human decidua, are required.

The present study demonstrated that both L-dopa and dopamine stimulated the synthesis of prostaglandins by human decidua vera. We suggest that increasing amniotic fluid dopamine and L-dopa near term stimulate prostaglandin production by fetal membranes.

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