

The Sympathomimetic Actions of *l*-Ephedrine and *d*-Pseudoephedrine: Direct Receptor Activation or Norepinephrine Release?

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The basic mechanisms by which ephedrine is preferred over other vasopressors in obstetric anesthesia have not been clearly defined. We examined the sympathomimetic effects of *l*-ephedrine, currently used as a vasopressor, and *d*-pseudoephedrine, currently used as a decongestant. In anesthetized rats, *l*-ephedrine and *d*-pseudoephedrine caused dose-dependent increases in arterial blood pressure and heart rate, and these effects disappeared after destruction of the sympathetic nerve terminals with 6-hydroxydopamine (6-OHDA) pretreatment. The two ephedrine isomers produced concentration-dependent increases in tension of anococcygeal muscle and sinus rate of right atrium from rats. However, the anococcygeal and atrial responses to *d*-pseudoephedrine

were abolished after 6-OHDA pretreatment, whereas approximately 50% of the responses to *l*-ephedrine were 6-OHDA-resistant. In human umbilical artery and vein, the two isomers failed to generate any contraction when given at the concentration that is capable of producing significant effects on anococcygeal and atrial tissues. Although direct adrenoceptor activation with *l*-ephedrine was detectable at tissue levels, the pressor response *in vivo* was entirely attributable to norepinephrine release from sympathetic nerves. This indirect mechanism could partly explain why *l*-ephedrine is better at increasing maternal arterial blood pressure while preserving the uteroplacental blood flow that is devoid of the involvement of the sympathetic innervation.

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Ephedrine is one of the most commonly used sympathomimetic drugs in the practice of anesthesia (1). Its stimulant actions result from direct and indirect activation of α - and β -adrenoceptors (2,3). The major mechanism of its indirect action is considered to

be release of norepinephrine from peripheral sympathetic neurons and, possibly, inhibition of neuronal norepinephrine reuptake, rather than a centrally mediated action (4). In obstetric anesthesia, ephedrine is used to treat hypotension that may occur with spinal anesthesia because it preserves the uteroplacental blood flow (5,6). Despite the wide acceptance of ephedrine as the vasopressor of choice for obstetric anesthesia, its superiority over other vasopressors with α -adrenergic activity (e.g., phenylephrine, metaraminol) has not been clearly defined. The experiments using uterine and femoral arteries from pregnant sheep have suggested that ephedrine may spare uterine perfusion during pregnancy because of more selective constriction of systemic vessels than that caused by metaraminol (7). However, whether the indirectly sympathomimetic property of ephedrine is important in the regional difference in the vascular action of ephedrine between systemic and uteroplacental vessels is unknown.

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Because ephedrine contains two asymmetrical carbon atoms, four stereoisomers of ephedrine are present: *l*-ephedrine, *d*-ephedrine, *l*-pseudoephedrine, and *d*-pseudoephedrine (8). The pharmacological properties of the four stereoisomers may be quite different from each other. Among these stereoisomers only *l*-ephedrine is used as a vasopressor in the practice of anesthesia; however, *d*-pseudoephedrine can also be used clinically. It is also widely used to relieve nasal congestion (9,10) and is the preferred decongestant for pregnant patients (11). The current study was designed to pharmacologically characterize the sympathomimetic actions of two stereoisomers of ephedrine that are now clinically available, *l*-ephedrine and *d*-pseudoephedrine, using intact animals and isolated tissues. From the present results, we propose that the indirectly sympathomimetic property of *l*-ephedrine may be one of the potential mechanisms to explain the usefulness for *l*-ephedrine on treatment of hypotension during pregnancy.

Methods

All experimental procedures were performed in accordance with the "Guiding Principles for Research Involving Animals and Human Beings" of Yokohama City University School of Medicine, Yokohama, Japan, and under the regulation laid down by the Hokkaido University School of Medicine Animal Care and Use Committee, Sapporo, Japan.

Male Wistar rats (200–300 g) were anesthetized with pentobarbital (30 mg/kg IV). The animal was ventilated with an artificial respirator after tracheostomy according to the following formula: body weight (g) \times 0.01 mL. Mean arterial blood pressure (MAP) and heart rate (HR) were continuously monitored from a cannulated femoral artery by using a pressure transducer. *l*-Ephedrine, *d*-pseudoephedrine, and phenylephrine were administered IV through a catheter inserted into the tail vein. Each vasopressor was prepared in normal saline. Baseline values were defined as the average values (obtained from 3 consecutive recordings at 3–4 min increments) for the 10-min period immediately before dosing. After a 20-min equilibration period, each animal received 3 consecutive bolus injections of the test drugs at 10–15 min intervals. This dosing cycle allowed the hemodynamic effect of the individual dose to return to baseline values before injection of the next dose. Three animals received normal saline alone as time and volume controls. Appropriate injections of normal saline had only minimal effects on hemodynamic variables.

The systemic administration of 6-hydroxydopamine (6-OHDA) produces selectively a subtotal destruction of the sympathetic nerve terminals (12,13). Rats were given 100 mg/kg of 6-OHDA IP on the first day and 250 mg/kg on the second day. The animals were killed

for the experiments 18 to 24 h after the last dose of 6-OHDA. Treatment of rats with 6-OHDA produced a loss in body weight of approximately 20%, whereas untreated animals showed a slight increase in body weight over the 3-day treatment period. 6-OHDA, 100 mg/mL, was dissolved in 0.9% NaCl containing 1% ascorbic acid. The effectiveness of this 6-OHDA treatment in destroying sympathetic nerve terminals was confirmed by the finding that the stimulatory effects of tyramine, which releases norepinephrine by stoichiometric displacement after being taken up into sympathetic nerve endings (14), were nearly completely abolished in a series of experiments performed in this study.

Rats were killed by exsanguination under anesthesia with gaseous diethyl ether. The hearts were quickly removed and transferred to a dissection bath filled with oxygenated Krebs-Henseleit solution. The composition of the solution was: 119 mM NaCl, 4.8 mM KCl, 1.2 mM MgSO₄, 1.2 mM KH₂PO₄, 2.0 mM CaCl₂, 24.9 mM NaHCO₃, and 10.0 mM glucose. The spontaneously beating right atrium was carefully dissected from the heart. The right atrium was suspended in a 10-mL water-jacketed bath containing Krebs-Henseleit solution gassed with 95% O₂ and 5% CO₂. The resting tension applied to the preparation was adjusted to 1 g. The bath was kept at a temperature of 36°C. The spontaneous rate was determined by counting the mechanical activity, which was monitored with a transducer. Each preparation was equilibrated for at least 60 min before construction of the cumulative concentration-response curves for test drugs. At completion of the concentration-response curve for *l*-ephedrine or *d*-pseudoephedrine, isoproterenol at 100 nM (a concentration producing maximal response for isoproterenol) was applied to the preparation. The results were expressed as a percentage of the maximal increase in the sinus rate induced by 100 nM isoproterenol.

A pair of anococcygeal muscles were dissected from the rat according to the method described by Gillespie (15). The muscle was mounted vertically in a water-jacketed chamber filled with 25 mL of Krebs-Ringer solution that was gassed with 95% O₂/5% CO₂ and maintained at 36°C. The composition of the solution was as follows: 119 mM NaCl, 4.5 mM KCl, 0.5 mM MgCl₂, 1.2 mM NaH₂PO₄, 2.5 mM CaCl₂, 24.9 mM NaHCO₃, and 11.0 mM glucose. The muscle was stretched to a resting tension of 1 g (the point where maximal contraction to 30 μ M phenylephrine occurred) and then allowed to equilibrate for at least 60 min. Force generation was monitored by an isometric transducer, and the output of the force transducer was registered on a pen recorder. After the equilibration period, the muscles were repeatedly challenged with 30 μ M phenylephrine until contractions reached a constant maximal value. To establish concentration-response curves, the cumulative doses of test drugs were applied. After completion of the concentration-response curve for *l*-ephedrine or

d-pseudoephedrine, the muscle was thoroughly washed with Krebs-Ringer solution and was exposed to 30 μ M phenylephrine. The results were expressed as a percentage of the maximal contraction induced by phenylephrine at 30 μ M (a concentration producing maximal response for phenylephrine).

Human umbilical cords were obtained at cesarean deliveries from healthy Japanese women between the 37th and the 38th wk of gestation after approval of the Ethics Committee of Hokkaido University Hospital. Segments of umbilical arteries and veins were carefully dissected from the cords and were cut into rings 5 mm in length. Rings were placed in a water-jacketed chamber filled with 25 mL of Krebs-Ringer solution. The solution in the chamber was gassed with 95% O₂/5% CO₂, and its temperature was maintained at 36°C. Each ring was suspended by a pair of stainless steel hooks under a resting tension of 2 g. The resting tension was confirmed to be the optimal resting preload for the vessel. Isometric tension was monitored with a transducer and recorded on a pen recorder. The rings were allowed to equilibrate for at least 60 min before the start of recordings. The rings were repeatedly challenged with 60 mM K⁺ until reproducible contractile response was obtained. This procedure ensured that the preparation had stabilized before the challenge with test drugs. Then, the vessel was exposed to 10 μ M *l*-ephedrine or 10 μ M *d*-pseudoephedrine for the appropriate time. When each challenge was complete, the vessel was thoroughly washed with Krebs-Ringer solution. Finally, the vessel was exposed to 10 μ M phenylephrine, which consistently produced contraction.

l-Ephedrine hydrochloride and *d*-pseudoephedrine hydrochloride were donated by Alps Pharmaceutical Industries (Gifu, Japan). 6-OHDA hydrochloride, tyramine hydrochloride, *l*-isoproterenol hydrochloride, *l*-phenylephrine hydrochloride, *l*-norepinephrine hydrochloride, and *dl*-propranolol hydrochloride were purchased from Sigma Chemical (St. Louis, MO). Prazosin hydrochloride was a gift from Pfizer Pharmaceutical (Tokyo, Japan) and atenolol was obtained from AstraZeneca Pharmaceutical (Osaka, Japan).

Data are expressed as means \pm SD. Statistical assessment of the data was made by Student's *t*-test for unpaired data or one-way analysis of variance followed by the Scheffé multiple comparison test to locate differences between groups. Nonparametric data were analyzed by the Mann-Whitney *U*-test or Wilcoxon's signed rank test. A significant difference was assumed to exist if the *P* value was <0.05.

Results

MAP and HR in Anesthetized Rats

The vasopressor and tachycardiac effects of *l*-ephedrine and *d*-pseudoephedrine were evaluated in anesthetized

rats with and without 6-OHDA pretreatment. After cannulations and equilibration, the baseline MAP and HR of anesthetized, untreated rats before drug administration were 113 \pm 13 mm Hg and 398 \pm 37 bpm (*n* = 11), respectively. Both *l*-ephedrine and *d*-pseudoephedrine increased MAP and HR on IV injection into anesthetized, untreated rats in a dose-related manner (Fig. 1). The peak responses of MAP and HR were achieved with the largest dose of each ephedrine isomer. Thus, *l*-ephedrine was approximately 3 times more potent than *d*-pseudoephedrine in inducing vasopressor and tachycardiac responses in untreated rats. In 6-OHDA-pretreated animals, resting MAP (76 \pm 6 mm Hg) and HR (255 \pm 17 bpm, *n* = 3) were much less, relative to untreated animals. The two ephedrine isomers produced virtually no pressor and tachycardiac response in 6-OHDA-pretreated animals (*n* = 3). In untreated rats, phenylephrine, a full α_1 -adrenoceptor agonist, elicited a maximal increase in MAP of 71 \pm 24 mm Hg (*n* = 5) at 4.2 μ g/kg but caused a marked decrease in HR (-50 ± 29 bpm). The effect of phenylephrine on MAP and HR in 6-OHDA-pretreated animals was essentially the same as that obtained in untreated animals: it produced a dose-dependent pressor effect and bradycardia over a similar dose range in untreated animals.

Positive Chronotropic Responses of Rat Right Atrium

The positive chronotropic activities of *l*-ephedrine and *d*-pseudoephedrine in right atria from untreated and 6-OHDA-pretreated rats were examined in comparison with that of isoproterenol. The basal rate of spontaneously beating right atria from untreated animals was 275 \pm 19 bpm (*n* = 22). Pretreatment with 6-OHDA resulted in a small but significant reduction in the basal rate (245 \pm 31 bpm, *n* = 15, *P* < 0.05). Isoproterenol, *l*-ephedrine, and *d*-pseudoephedrine all caused an increase in the spontaneous rate of untreated atria in a concentration-dependent manner (Fig. 2). After 6-OHDA pretreatment, the concentration-response curve for isoproterenol was significantly displaced to the right, the EC₅₀ values being reduced from 1.0 \pm 0.4 nM to 2.2 \pm 1.2 nM (*n* = 6, *P* < 0.05). However, the maximum rate increases in response to isoproterenol, measured in absolute units, did not differ significantly between atria from untreated and 6-OHDA-pretreated animals (136 \pm 23 versus 113 \pm 21 bpm). *l*-Ephedrine and *d*-pseudoephedrine both were full agonists (the efficacy can be set equal to 1) in right atria, the maximum rate increases of right atria from untreated animals being 96% \pm 12% (*n* = 7) and 93% \pm 9% (*n* = 7) of the isoproterenol maximum, respectively, although *l*-ephedrine was 6 times more potent than *d*-pseudoephedrine as assessed by the EC₅₀ values (1.8 \pm 0.6 versus 10.6 \pm 8.1 μ M). When rats were pretreated with 6-OHDA, the maximum response to

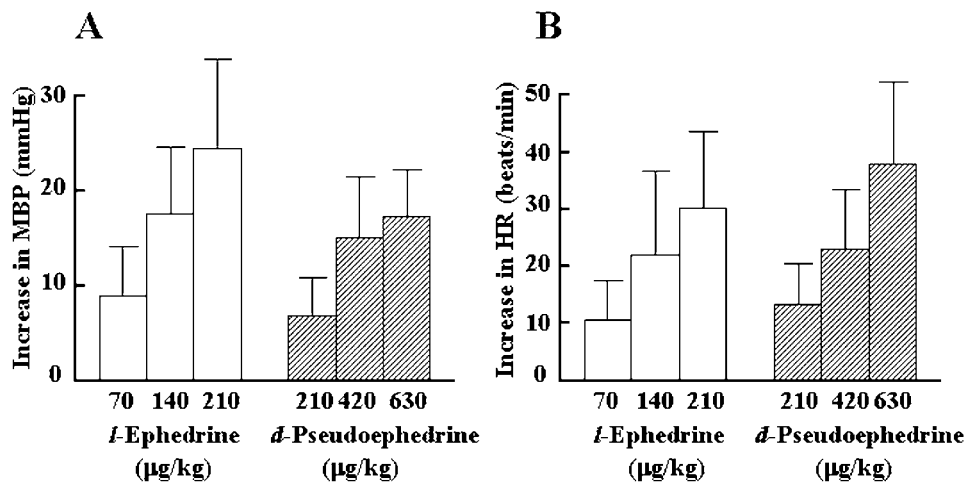


Figure 1. Increases in mean arterial blood pressure (MAP) (A) and heart rate (HR) (B) produced by *l*-ephedrine and *d*-pseudoephedrine administered IV to anesthetized rats. Data are presented as mean \pm SD ($n = 7$).

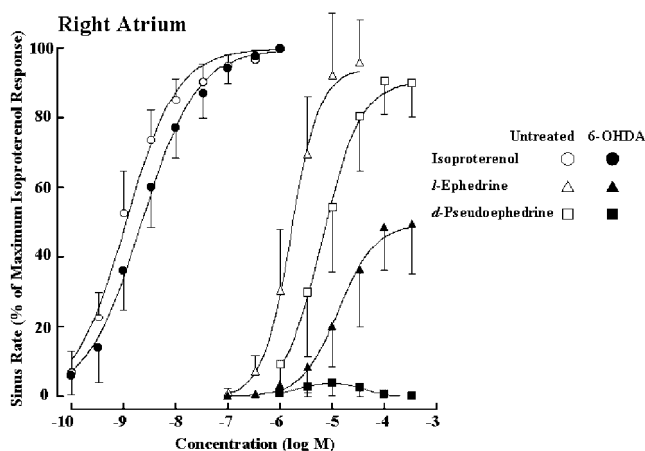


Figure 2. Concentration-response curves for the positive chronotropic effects of isoproterenol (circles), *l*-ephedrine (triangles), and *d*-pseudoephedrine (squares) in spontaneously beating right atria from untreated (open symbols) and 6-OHDA-pretreated (closed symbols) rats. Responses were measured as the increase in spontaneous rate above the resting level and plotted as a percentage of the maximum response to isoproterenol. Data are presented as mean \pm SD ($n = 3-8$).

l-ephedrine was markedly decreased to $51\% \pm 14\%$ ($n = 6$, $P < 0.01$). In addition, the EC_{50} value was significantly increased to $19.3 \pm 15.2 \mu\text{M}$ ($n = 6$, $P < 0.05$) after 6-OHDA pretreatment. This positive chronotropic effect of *l*-ephedrine observed in 6-OHDA-pretreated atria was nearly completely eliminated by $1 \mu\text{M}$ propranolol, a nonselective β -adrenoceptor antagonist, or $10 \mu\text{M}$ atenolol, a selective β_1 -adrenoceptor antagonist ($n = 3$ for each). However, *d*-pseudoephedrine failed to evoke any increase in the sinus rate of atria from 6-OHDA-pretreated animals ($n = 3$).

Contractile Responses of Rat Anococcygeal Muscle

Concentration-response curves were obtained for contractions induced by phenylephrine, *l*-ephedrine, and

d-pseudoephedrine in rat anococcygeal muscle (Fig. 3). *l*-Ephedrine behaved as a full agonist on this preparation, the maximum contraction of the anococcygeal muscle ($115\% \pm 16\%$ of the maximum phenylephrine response, $n = 6$) being identical to that of phenylephrine. When anococcygeal muscle preparations from untreated rats and those receiving 6-OHDA by the IP route were compared, the maximum response to *l*-ephedrine was markedly reduced to $57\% \pm 3\%$ of the maximum contraction to phenylephrine ($n = 4$, $P < 0.05$) by 6-OHDA pretreatment. In addition, there was an evident rightward shift of the concentration-response curve for *l*-ephedrine with a significant increase in the EC_{50} value of $34.4 \pm 16.1 \mu\text{M}$ ($n = 4$) after 6-OHDA pretreatment when compared with untreated preparations ($2.4 \pm 0.3 \mu\text{M}$, $n = 6$, $P < 0.05$). The contractile response to *l*-ephedrine observed in 6-OHDA-pretreated anococcygeal muscle was completely eliminated by $1 \mu\text{M}$ prazosin, an α_1 -adrenoceptor antagonist ($n = 3$). *d*-Pseudoephedrine behaved as a partial agonist, the maximum response being $56\% \pm 16\%$ ($n = 6$) relative to the phenylephrine maximum. The EC_{50} value ($11.3 \pm 5.1 \mu\text{M}$, $n = 6$) for *d*-pseudoephedrine was significantly larger than the value for *l*-ephedrine ($P < 0.01$). After pretreatment with 6-OHDA, *d*-pseudoephedrine failed to generate any contraction of rat anococcygeal muscle ($n = 4$). Although 6-OHDA pretreatment apparently resulted in a small leftward shift of the concentration-response curve for phenylephrine, there was no significant difference in the sensitivity or the maximum response to phenylephrine between anococcygeal muscle preparations from untreated and 6-OHDA-pretreated animals.

Contractile Responses of Human Umbilical Artery and Vein

Reproducible contractile effects were recorded when human umbilical artery was exposed to 60 mM K^+ ($n = 4$, Fig. 4A). However, the addition of *l*-ephedrine or

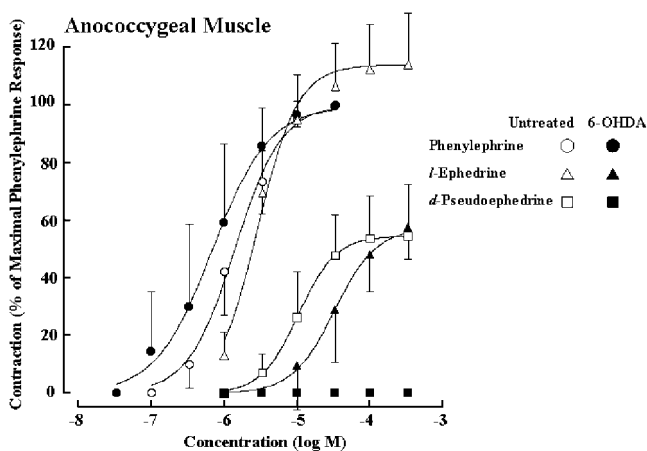


Figure 3. Concentration-response curves for the contractile effects of phenylephrine (circles), *l*-ephedrine (triangles), and *d*-pseudoephedrine (squares) in anococcygeal muscles from untreated (open symbols) and 6-hydroxydopamine (6-OHDA)-pretreated (closed symbols) rats. Responses were measured as the increase in tension from the resting level and expressed as a percentage of the maximum responses to phenylephrine. Data are presented as mean \pm SD ($n = 4-11$).

d-pseudoephedrine at a concentration of 10 μ M failed to generate any contraction. When 10 μ M phenylephrine was given, a sharp and immediate increase in tension was observed. Similar results were obtained with human umbilical veins ($n = 4$, Fig. 4B). Neither human umbilical artery nor vein responded to 100 μ M tyramine.

Discussion

Ephedrine is generally described as an indirectly acting sympathomimetic amine with some degree of direct actions on adrenoceptors (2,3). This spectrum of sympathomimetic activity ranging from direct to indirect, together with four stereoisomers of this sympathomimetic drug (8), could provide widely different aspects of pharmacological effects of these ephedrine isomers on various tissues. In this study, we evaluated the sympathomimetic effects of *l*-ephedrine and *d*-pseudoephedrine, the currently available ephedrine isomers as vasopressor and decongestant, respectively, on MAP (α_1) and HR (β_1) in intact animals, sinus rate (β_1) in isolated rat right atrium, and tension development (α_1) in isolated rat anococcygeal muscle and human umbilical vessels.

In anesthetized rats, both ephedrine isomers elicited dose-dependent pressor effects, although *l*-ephedrine proved 3 times more potent than *d*-pseudoephedrine. The effects of the two ephedrine isomers on HR roughly paralleled their pressor effects. When the animals were pretreated with 6-OHDA, which selectively produces a subtotal destruction of the sympathetic nerve terminals (12,13), the effects of

l-ephedrine and *d*-pseudoephedrine to increase MAP and HR were completely eliminated. This suggests that the sympathomimetic effects of *l*-ephedrine and *d*-pseudoephedrine are entirely attributable to norepinephrine release from sympathetic nerve endings under *in vivo* conditions. In this series of experiments, *l*-ephedrine was administered to the rat by rapid IV injection at 70–210 μ g/kg. The clinically used doses lie within the chosen dose range.

Interpretation of the actions of the two ephedrine isomers on cardiac β_1 -adrenoceptors may be complicated by diverse results from different experimental models used in the present study. Although both *l*-ephedrine and *d*-pseudoephedrine acted on the spontaneous rate of isolated rat right atrium as full agonists and the positive chronotropic effect of *l*-ephedrine was in part attributable to direct activation of β_1 -adrenoceptors, the moderate increase in HR by IV injection of each ephedrine isomer into anesthetized rats was completely dependent on their norepinephrine-releasing action. However, the increase in HR caused by ephedrine isomers in intact animals may have been limited by other factors (e.g., changes in MAP). Indeed, increasing MAP with phenylephrine resulted in a marked reduction in HR. Direct activation of β_1 -adrenoceptors with *l*-ephedrine is in good agreement with the result of Vansal and Feller (16), who have shown the direct interaction of *l*-ephedrine with human β_1 -adrenoceptors transfected in Chinese hamster ovary cells, with a 66% efficacy of isoproterenol.

In anococcygeal muscles isolated from rats, which are innervated abundantly by sympathetic nerves (15), *l*-ephedrine behaved as a full agonist. The potency and efficacy for *l*-ephedrine in inducing contractions in rat anococcygeal muscle were significantly decreased after pretreatment with 6-OHDA. However, approximately 50% of contractions remained in 6-OHDA-pretreated muscle. This remaining contractile response of 6-OHDA-pretreated muscle to *l*-ephedrine was completely blocked by 1 μ M prazosin. Thus, *l*-ephedrine is capable of producing contractions in rat anococcygeal muscle through direct activation of α_1 -adrenoceptors in addition to a release of norepinephrine from nerve endings. This result is in contrast to the findings from our intact animal experiments showing that the pressor activity of *l*-ephedrine disappeared completely after pretreatment of the rat with 6-OHDA. A possible explanation for this apparent discrepancy may be the fundamental difference between the blood vessels involved in MAP and the isolated anococcygeal muscle. It could be considered that α_1 -adrenoceptors on the vascular beds fail to react sensitively to *l*-ephedrine, resulting in no detection of direct activation of α_1 -adrenoceptors with *l*-ephedrine *in vivo*. Thus, α_1 -adrenoceptor subtypes involved in the pressor

A Human Umbilical Artery

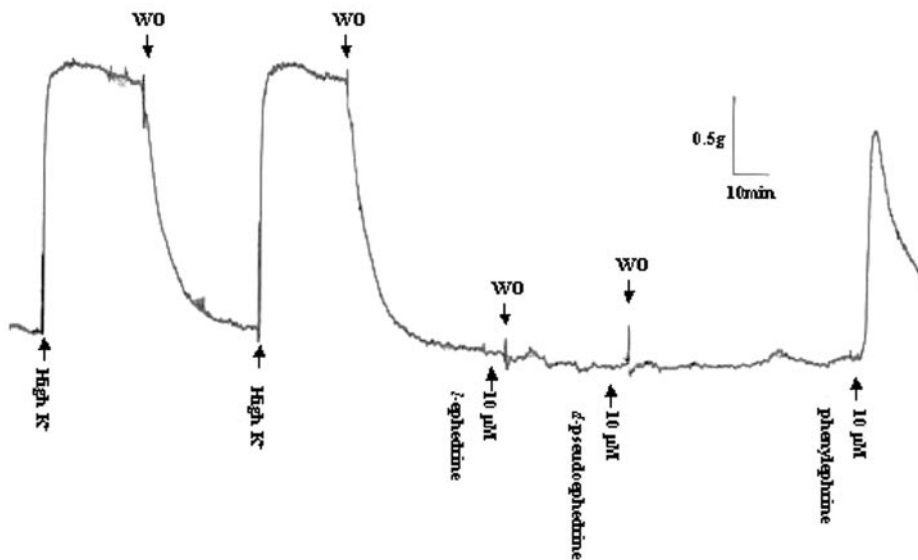
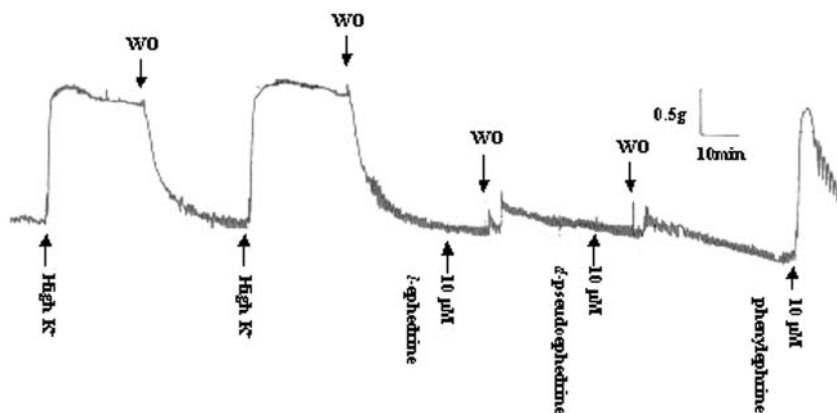


Figure 4. Effects of 10 μM *l*-ephedrine, 10 μM *d*-pseudoephedrine and 10 μM phenylephrine on vascular tone in human umbilical artery (A) and vein (B). For comparison, contractions induced by 60 mM K^+ (high K^+) are shown. WO = washout with drug-free normal Krebs-Ringer solution. Similar results are obtained with three other vessels of each type.

B Human Umbilical Vein



response *in vivo* and the contractile response of anococcygeal muscle may be different. α_1 -Adrenoceptors are a heterogeneous group of receptors and have been subclassified into α_{1A} , α_{1B} , and α_{1D} -adrenoceptor subtypes based on radioligand binding, molecular biology, and isolated tissue experiments (17). It has been reported that vascular α_{1D} -adrenoceptors play a role in pressor responses *in vivo* (18). Although the distribution of α_1 -adrenoceptor subtypes in rat anococcygeal muscle remains poorly characterized, the α_1 -adrenoceptor subtype mediating contractions in this tissue might be inferred as being *via* a population of α_{1A} - or α_{1B} -subtypes. However, it remains to be determined whether there are differences in the affinities of different α_1 -adrenoceptor subtypes for *l*-ephedrine.

d-Pseudoephedrine was a partial agonist in anococcygeal muscle. When the animals were pretreated with

6-OHDA, *d*-pseudoephedrine no longer generated contraction in this tissue. It is thus likely that the contractile effect of *d*-pseudoephedrine in this tissue is exclusively attributable to norepinephrine release from sympathetic nerve endings. Alternatively, it may be suggested that *d*-pseudoephedrine has no ability to activate α_1 -adrenoceptors directly.

Ephedrine is usually recommended as the first-line vasopressor to treat hypotension associated with spinal anesthesia in obstetrics. This is because ephedrine is superior to other vasopressors in preserving the uteroplacental blood flow (5,6). It should be noted that the uteroplacental circulation lacks, or at least reduces, the sympathetic innervation compared with the nonpregnant uterine circulation (19-21). In the present study, we showed that despite *l*-ephedrine, the only ephedrine isomer used clinically as a vasopressor at present, causing

direct activation of α_1 - and β_1 -adrenoceptors in isolated tissues and cells, its pressor response was entirely attributable to norepinephrine release from sympathetic nerve terminals under *in vivo* conditions. Importantly, we observed that neither *l*-ephedrine nor *d*-pseudoephedrine generated any contraction in human umbilical artery and vein at the concentration to cause a norepinephrine-releasing action in atrial and anococcygeal muscles. Thus, it could be supposed that *l*-ephedrine has little effect on the uteroplacental circulation. Consequently, it may be expected to shift the blood flow abundantly from peripheral tissues innervated by the sympathetic nerves to the placenta when *l*-ephedrine is given. However, the present experiments do not provide crucial evidence for the safety of *l*-ephedrine in pregnancy, as it cannot be determined whether *l*-ephedrine is also without effect on maternal uterine blood flow because of its indirectly sympathomimetic property. We also demonstrated that the sympathomimetic actions, including vasopressin, of *d*-pseudoephedrine were primarily the result of norepinephrine release. This could provide basic evidence for the choice of *d*-pseudoephedrine as the preferred decongestant during pregnancy to reduce potential cardiovascular adverse reactions in the fetus (11).

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