L-DOPA inhibits nitric oxide-dependent vasorelaxation via production of reactive oxygen species in rat aorta

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Abstract : Objectives : To clarify the underlying mechanisms of L-DOPA induced vasoconstriction in rat aorta. Methods : The effect of L-DOPA on phenylephrine-induced contractile force of blood vessels was examined in vitro using rat aortic ring preparations by isometric tension experiment. Involvement of nitric oxide (NO) in the effect of L-DOPA on vascular smooth muscle was studied by using Nω-Nitro-L-arginine (L-NNA), Sodium nitroprusside (SNP) in endothelium-intact and endothelium-denuded aortic rings. Results : L-DOPA potentiated α-adrenergic receptor- and depolarization-induced vascular contraction and inhibited acetylcholine-induced vasorelaxation. This effect was diminished by pretreatment of the aortic rings with L-NNA, an inhibitor of NO synthesis, or by removing the endothelium from the ring preparations. In endothelium-denuded rings, L-DOPA inhibited exogenous NO-dependent but not cGMP-mediated vasorelaxation. Increases in cGMP levels in response to an NO donor were attenuated by L-DOPA in cultured rat aortic smooth muscle cells. L-DOPA could not contract rings (without endothelium) pretreated with 3-(5'-hydroxymethyl-2'-furyl)-1-benzyl indazole (YC-1), an activator of guanylyl cyclase, but SOD (150 U/ml) pretreatment of rings with endothelium inhibited contraction by L-DOPA. Conclusions : These results suggest that L-DOPA inhibits nitric-dependent vasorelaxation on vascular smooth muscle cells via production of reactive oxygen species.


Keywords : L-DOPA, aortic rings, nitric oxide, vasorelaxation, reactive oxygen species

INTRODUCTION

L-DOPA (L-3,4-dihydroxyphenylalanine) is a widely used drug for the treatment of Parkinson’s disease (PD) (1, 2). Many studies showed that some doses of L-DOPA caused hypertensive response in human and laboratory animals. Early study reported that injection of L-DOPA could cause the cat renal hypertension (3), and that conscious rats orally administered L-DOPA following parenteral administration (4) and intraperitoneal administration of L-DOPA showed hypertensive responses (5). Intravenous L-DOPA evoked some tachycardia (2) and larger rises in blood pressure in human (6). However, these studies did not show precise mechanism of L-DOPA-induced hypertensive response. It has been known that tension in aortic vascular smooth muscle induced by either α-adrenergic agonists or
passive external stretch is related to NO release from the endothelium (7-9). On the other hand, phenylephrine induces NO release by $\alpha_2$ receptor in endothelium cells (10), in addition to direct contraction effect on smooth muscle. These NO-releasing systems of the vasculature is considered to function as a kind of self-protecting mechanism against excessive force generation by vascular smooth muscle cells (7). However, whether hypertensive effect of L-DOPA is related with NO signaling pathway is unknown. In this study, we investigated the mechanism of effect of L-DOPA on phenylephrine-induced contractile force of blood vessels in vitro by using several pharmacological blockers. The results indicate that the effect of L-DOPA on contractile force of blood vessels was mediated by NO signaling pathway via production of reactive oxygen species.

**METHODS**

**Agents**

Phenylephrine (phe), acetylcholine (Ach), sodium nitroprusside (SNP), S-nitroso-N-acetyl-penicillamine (SNAP), L-3,4-dihydroxyphenylalanine (L-DOPA), N-$\omega$-Nitro-L-arginine (L-NNA), 8-(4-chlorophenylthio) guanosine 3'5'-cyclic monophosphate (cpt-cGMP), 3-(5'-hydroxymethyl-2'-furyl)-1-benzyl indazole (YC-1), superoxide dismutase (SOD) and indomethacin were purchased from Sigma (St. Louis, MO, USA).

**Preparation of aortic rings and tension measurement**

All animal procedures were in accordance with the institutional guidelines for the care and use of laboratory animals of Tokushima University. Male Wistar rats (Japan SLC, Shizuoka, Japan) weighing 150-250 g were anesthetized by an intraperitoneal injection of pentobarbital. The thoracic aortas were dissected free of connective tissue and cut into ring segments, 3- to 4- mm in length. In some experiments, the aortic endothelium was removed by inserting a cotton thread into the lumen followed by gentle rubbing. Each ring was then placed in a 3 ml organ bath (Micro Easy Magnus, Kishimoto Medical; Kyoto, Japan) and mounted on two stainless steel wires, one of which was fastened to the bath and the other connected to a force transducer for the measurement of isometric tension. The bath was filled with Krebs-Ringer bicarbonate buffer (KRB) solution at 37°C and bubbled with a mixture of 95% O$_2$-5% CO$_2$. The KRB contained (in mmol/L) 118 NaCl, 4.6 KCl, 2.5 CaCl$_2$, 24.8 NaHCO$_3$, 1.2 MgSO$_4$, 1.2 KH$_2$PO$_4$, and 5.6 glucose. The ring was equilibrated for 60 mins under a resting tension of 1.5 g and the solution was changed at 30 min intervals. The presence or absence of endothelium was confirmed by the addition of the endothelium-dependent vasodilator, acetylcholine (10$^{-6}$ M), after contractions had been induced by phenylephrine ($\alpha_1$-adrenergic receptor agonist) (10$^{-6}$ M). Following washout of phenylephrine and acetylcholine with KRB, the aortic rings were contracted by adding a solution to the bath with a high K$^+$ concentration (50 mM KCl). After recording the contractile force of each ring in response to high K$,^+$ the KCl was washed out with KRB. Each ring was then allowed to equilibrate at a resting tension of 1.5 g for 20 min. The contractile response in the test experiments described below was expressed relative to that measured for the KCl-induced contraction (1st KCl) (11, 12).

**Preparation of rat smooth muscle cells**

Isolation of vascular smooth muscle cells from rats was conducted as described previously (13). Briefly, male Wistar rats aged 8 to 10 weeks were anesthetized with ether, and 1.0 U/g heparin was injected into the peritoneal cavity 30 min before surgery. Aortas were dissected and longitudinally opened in the longitudinal direction, and endothelium and adventitia were removed. The tissue was then minced into small pieces in normal Tyrode’s solution. The pieces were then explanted on glass coverslips in tissue culture dishes filled with medium 199 (Nissui Chemicals, Tokyo, Japan), supplemented with 10% fetal bovine serum (GIBCO, Grand Island, NY), 100 $\mu$g/ml streptomycin, and 100 $\mu$g/ml penicillin and stored in a carbon dioxide incubator (5% CO$_2$, 37°C). Single smooth muscle cells migrated out of the tissues and adhered to the coverslips within a few days. After culturing for 6-10 days, they were used in the experiments described below.

**Effect of L-DOPA on aortic ring contraction**

Test experiments involving L-DOPA were conducted on aortic rings in which contraction was induced by either phenylephrine (10$^{-9}$-10$^{-4.5}$ M) or KCl (30, 50, or 80 mM). L-DOPA (10$^{-7}$ to 10$^{-4.5}$ M) was added to the incubation system either 20 min prior to or during the contraction induced by each constrictor. Vehicle (water)-treated rings were used as controls.
NO synthesis Inhibitor treatment of aortic rings

In some experiments, endothelium-derived nitric oxide (NO) or prostaglandins were blocked by incubating aortic rings with L-NNA (3×10⁻⁵ M) or indomethacin (10⁻⁵ M) to inhibit NO or prostaglandin synthesis, respectively. The aortic rings were pretreated with each inhibitor for 20 min and then contraction was induced by phenylephrine or KCl. Each inhibitor was present in the incubation system during contraction.

Determination of L-DOPA-inhibited endothelium-dependent aortic relaxation

In the experiment of effect of SNP, cpt-cGMP or acetylcholine, SNP (NO donor; 10⁻¹⁰⁻10⁻⁶ M) or cpt-cGMP (10⁻⁹⁻10⁻⁴ M) were added to the bath during the contraction induced by phenylephrine (10⁻⁵ M) or KCl (50 mM). In other experiments, acetylcholine (10⁻⁶ M)-induced vasorelaxation was assessed in aortic rings that had been contracted by phenylephrine (10⁻⁵ M).

Effect of YC-1 on L-DOPA-inhibited relaxation of aortic rings

Aortic rings without endothelium pretreated with L-DOPA (10⁻⁵ M) for 20 mins and then induced contraction by phenylephrine (10⁻⁵ M). YC-1 (0.1-100 μM) per 10 mins added into the bath with the subsequent contraction by phenylephrine. Vehicle (water)-treated rings were used as controls.

Effect of SOD on L-DOPA-inhibited endothelium-dependent relaxation of aortic rings

Aortic rings with endothelium were pretreated with SOD (150 U/ml) for 20 mins and then induced contraction by phenylephrine (10⁻⁵ M). L-DOPA (10⁻⁷⁻10⁻⁴.5 M) were added to the bath after induced contraction. Vehicle (water)-treated rings were used as controls.

Measurement of intracellular cGMP

The rat smooth muscle cells cultured in a 35 mm dish were treated with or without L-DOPA (10⁻⁵ M) in the Krebs-Ringer Hepes buffer solution (containing 125 mM NaCl, 5 mM KCl, 1.8 mM CaCl₂, 2.6 mM MgSO₄, and 5 mM Hepes, pH 7.4) for 5 min at 37°C. Cells were then stimulated with SNAP (1, 10, or 100 M) for 5 mins. Following washing two times with ice-cold phosphate-buffered saline, intracellular cGMP was extracted with 1 ml of HCl (0.1 M) under shaking for 20 minutes at room temperature. The extracted solution was centrifuged at 80× g for 5 minutes. The concentration of cGMP in the supernatant was measured with a cGMP EIA kit (Cayman Chemical, Michigan, USA) according to the manufacturer’s protocol. The concentration of intracellular cGMP was expressed as pmol per mg protein.

Statistical analysis

Data are expressed as the mean±S.D. and were analyzed by ANOVA plus Bonferroni multiple comparison tests. A P-value<0.05 was regarded as statistically significant.

RESULTS

L-DOPA potentiated phenylephrine-induced contraction through endothelium- and NO-dependent pathways

Firstly, we examined the effect of L-DOPA on vascular contraction using rat aortic rings precontracted by phenylephrine (Fig. 1-a). Fig. 1-b showed a trace demonstrating the effect of L-DOPA on rat aortic rings pretreated with phenylephrine. As shown in Fig. 1-c, administration of L-DOPA alone to the rings without phenylephrine (vehicle group) did not induce contraction. However, when the rings were precontracted by phenylephrine, subsequent administration of L-DOPA potentiated contraction in a dose-dependent manner. After washed with KRB, the contractile effect of the rings caused by L-DOPA disappeared and L-DOPA retreatment restored rat aortic ring contraction to phenylephrine precontraction state. This effect of L-DOPA was not affected by pretreatment of the rings with indomethacin (10⁻⁵ M), an inhibitor of prostaglandin synthesis (Fig. 1-c). In contrast, pretreatment of the rings with L-NNA (3×10⁻⁵ M), an inhibitor of NO synthesis, or the removal of endothelium from the rings (Fig. 1-d) significantly inhibited the L-DOPA-mediated increase in contractile force. Dopamine and its metabolite, DOPAC (L-3,4-dihydroxyphenylactic-acid), failed to enhance the phenylephrine-induced aortic contraction when these substances were used at concentrations up to 10⁻⁵ M (data not shown).

To examine the effect of L-DOPA pretreatment on subsequent phenylephrine-induced contraction, L-DOPA (10⁻⁵ M) was administrated 20 min prior to phenylephrine (10⁻⁶⁻10⁻⁵ M) (Fig. 2-a). As shown in Fig. 2-b, L-DOPA pretreatment potentiated the subsequent phenylephrine-induced contraction in rings.
Fig. 1  L-DOPA potentiated phenylephrine-induced contraction of rat aortic rings through endothelium- and NO- dependent pathways (I). (a) Experimental design. L-DOPA (10^{-7} - 10^{-4.5} M) was administrated cumulatively to endothelium-intact/-denuded aortic rings which had been pretreated with or without (vehicle) phenylephrine (10^{-5} M). In some groups, L-NNA (3 \times 10^{-5} M) and/or indomethacin (Indo ; 10^{-5} M) were administrated to the aortic rings 20 min prior to phenylephrine (or vehicle) administration (inverted triangle). (b) Trace demonstrating the effect of L-DOPA on endothelium-intact rat aortic rings pretreated with phenylephrine. (c) Concentration-response curves for L-DOPA-induced change in the contractile force of endothelium-intact aortic rings. (d) Concentration-response curves for L-DOPA-induced change in the contractile force of endothelium-denuded aortic rings. Data are expressed as means ± S.D. for 4 aortic rings in each group. * \ p < 0.05 compared with vehicle group (open circles). † \ p < 0.05 compared with Phenylephrine group (closed circles).

Fig. 2  L-DOPA potentiated phenylephrine-induced contraction of rat aortic rings through endothelium- and NO- dependent pathways (II). (a) Experimental design. Phenylephrine (Phe : 10^{-9} - 10^{-4.5} M) was administrated cumulatively to endothelium-intact/denuded rat aortic rings which had been pretreated with or without (vehicle) L-DOPA (10^{-5} M). In some groups (panel c), L-NNA (3 \times 10^{-5} M) was administrated to the aortic rings together with L-DOPA (or vehicle) (inverted triangle). (b) Concentration-response curves for phenylephrine-induced changes in contractile force of endothelium-intact (E+) aortic rings. (c) Concentration-response curves for phenylephrine-induced change in contractile force of endothelium-intact (E+) aortic rings pretreated with L-NNA. (d) Concentration-response curves for phenylephrine-induced changes in contractile force of endothelium-denuded (E-) aortic rings. There are no difference between experimental group and control in (c) and (d). Data are expressed as means ± S.D. for 4 aortic rings in each group. * \ p < 0.05 compared with vehicle group (open circles).
with intact endothelium. It is well known that the blockade of endothelium-derived NO or removal of endothelium itself induces hypercontractility of blood vessels (11). L-DOPA pretreatment did not further increase contractile force in these NO-blocked and endothelium-denuded aortic rings (Fig. 2c and d). These results suggest that L-DOPA potentiated phenylephrine-induced aortic contraction through endothelium- and NO-dependent pathways.

We also examined the effect of L-DOPA on depolarization-induced contraction of rat aortic rings precontracted by KCl (50 mM). Administration of L-DOPA during KCl-induced contraction increased contractile force in a dose-dependent manner. This effect of L-DOPA was almost completely inhibited by pretreatment of the rings with L-NNA (3×10⁻⁵ M) as well as in the rings without endothelium (data not shown).

**L-DOPA inhibited endothelium-dependent relaxation of the aorta**

Next, we tested whether potentiation of L-DOPA is due to inhibition of endothelium-dependent relaxation by NO signal. The effect of L-DOPA on endothelium-dependent vasorelaxation was examined using aortic rings which had been precontracted by phenylephrine (Fig. 3-a). As shown in Fig. 3-b, acetylcholine (10⁻⁶ M) almost completely relaxed the tension in aortic ring with intact endothelium.

Since acetylcholine-induced vasorelaxation depends largely on endothelium-derived NO in conduit arteries (14), this relaxation was inhibited by pretreatment with L-NNA (Fig. 3-c). L-DOPA pretreatment also inhibited acetylcholine-induced vasorelaxation to the same extent as that observed in the L-NNA-treated rings (Fig. 3-c).

**L-DOPA inhibited exogenous NO-dependent but not cGMP-mediated vasorelaxation**

NO activates guanylate cyclase which in turn increases the concentration of intracellular cGMP in the smooth muscle cells (15). The rise of cGMP levels triggers subsequent vasorelaxation (15). To further study the mechanism of L-DOPA, we tested the effect of L-DOPA on cGMP induced vasorelaxation using the membrane-permeable cGMP analog, cpt-cGMP. Endothelium-denuded aortic rings were first precontracted by phenylephrine or KCl (Fig.

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![Fig. 3](image-url)  
**Fig. 3** L-DOPA inhibited acetylcholine-induced vasorelaxation in rat aortic rings. (a) Experimental design. Acetylcholine (ACh) (10⁻⁶ M) was administered to endothelium-intact aortic rings that had been precontracted by phenylephrine (Phe; 10⁻⁵ M). L-DOPA (10⁻⁵ M), L-NNA (3×10⁻⁵ M) or vehicle was administrated to the endothelium-intact aortic rings 20 min prior to phenylephrine administration. (b) Acetylcholine concentration induced maximum relaxation in endothelium-intact ring. Data are expressed as means±S. D. for 4 aortic rings in each group. * p<0.05 compared with vehicle group. (c) Acetylcholine-induced maximum relaxation in each endothelium-intact ring.
and after the contraction reached a steady level, subsequent relaxing responses induced by cpt-cGMP (10^-9 - 10^-4 M) were assessed in the presence or absence of L-DOPA (10^-5 M). L-DOPA pre-treatment failed to affect cpt-cGMP-mediated vasorelaxation in the rings contracted with phenylephrine (Fig. 4-b) or KCl (Fig. 4-c). L-DOPA-inhibited vasorelaxation was not soluble guanylyl cyclase-dependent

Soluble guanylyl cyclase (sGC) expressed by endothelium of blood vessel is considered the key enzyme mediating vascular relaxation induced by NO. By the formation of cyclic GMP, this enzyme mediates NO-mediated vascular smooth muscle relaxation (16, 17). In order to probe whether L-DOPA-inhibited vasorelaxation was caused by blocking the action of soluble guanylyl cyclase, effect of YC-1 (an activator of guanylyl cyclase) (18) on the aortic ring contraction was examined. In aortic rings without endothelium pretreatment with L-DOPA (10^-5 M), YC-1 was added into the bath and subsequent contraction effect of rings by phenylephrine was studied (Fig. 5-a). YC-1 (0.1 μM-100 μM) could relax the rings precontracted by phenylephrine in dose-dependent manner. There was no significant difference in relaxation between the ring with and without pretreatment by L-DOPA (Fig. 5-b), suggesting that soluble guanylyl cyclase is not a target of L-DOPA-inhibited vasorelaxation. Similar effect was observed in the experiment using atrial natriuretic peptide, an activator of membrane guanylyl cyclases (data not shown).

L-DOPA attenuates NO-donor-induced cGMP production in cultured rat aortic smooth muscle cells and inhibits acetylcholine-induced relaxation

To examine whether L-DOPA affects cGMP production by NO, cultured rat aortic smooth muscle cells were stimulated with a donor of NO, SNAP (1-100 μM), and intracellular cGMP levels were measured in the presence or absence of L-DOPA (10^-5 M).
M). As shown in Fig. 6, L-DOPA treatment inhibited cGMP production at higher SNAP concentrations. We also tested the effect of L-DOPA of exogenous NO on SNP-induced relaxation. The experimental design was showed by Fig. 7-a Namely the L-DOPA-Pretreatment endothelium-denuded aortic rings were precontracted by phenylephrine or KCl and then added SNP (NO donor) to observe L-DOPA attenuated effect on exogenous NO-dependent Vasorelaxation the results showed that L-DOPA pretreatment significantly attenuated vasorelaxation responses induced by SNP (10^{-11}-10^{-6} M) (Figs. 7-b and 7-c).

L-DOPA mediated inhibition of relaxation is due to inactivation of NO by oxygen free radicals

Increased production of reactive oxygen species (ROS) reduces the effect and/or bioavailability of NO, leading to an impaired endothelial function. Through auto-oxidation, L-DOPA forms reactive free radicals such as hydroxyl radicals, oxygen free radicals. Oxygen free radicals (O_2-) can decrease ring relaxation by inactivation of NO (19, 20). In this experiment we used SOD to decrease O_2- generation in order to further confirm NO effect in L-DOPA-mediated contraction. Aortic rings with endothelium were pretreated with SOD (150 u/ml) for 20 mins. L-DOPA (10^{-7}-10^{-5} M) were added to the bath with the subsequent contraction by phenylephrine (10^{-5} M) (Fig. 8-a). Fig. 8-b showed that SOD (150 U/ml) pretreatment inhibited contraction by L-DOPA of rings with endothelium.

DISCUSSION

Our present studies indicated that L-DOPA...
increased the α-adrenergic receptor-mediated and depolarization-induced vascular contraction and decreased ACh-induced vascular relaxation in endothelium-intact rat aorta, which was inhibited by L-NNA pretreatment. L-DOPA attenuated the rise in the intracellular cGMP and inhibited vasorelaxation with an NO donor, but not those with cpt-cGMP, a membrane-permeable cGMP analog, or YC-1, an activator of guanylyl cyclase, suggesting that production of reactive oxygen species by L-DOPA decreases the NO action. All these data demonstrated that the underlying mechanism of vaso-contractive effect of L-DOPA was inhibition of NO-dependent vasorelaxation via production of reactive oxygen species from L-DOPA.

It is well known that nitric oxide (NO) is the major mediator of endothelium-dependent relaxation in aorta (15, 21, 22), which is formed from the conversion of L-arginine by nitric oxide synthase (NOS) in endothelial cell and released. This endothelium-derived NO stimulates the activity of soluble guanylate cyclase (sGC) in smooth muscle cells, leading to an increase in cyclic guanosine-3'5'-monophosphate (cGMP) and finally to calcium depletion from the cytosolic space and vascular smooth muscle relaxation (15, 21-23). Various agonists such as NE (noradrenaline), phenylephrine, 5HT can stimulate the release of NO from the endothelium during vasoconstrictive response to them (9). In our present study, we found that L-DOPA increased the phenylephrine (α-adrenergic receptor)-mediated and depolarization-induced vascular contraction in endothelium-intact rat aorta, which was inhibited by L-NNA pretreatment, suggesting this reaction is mediated by NO pathway. Meanwhile, we also found that L-DOPA pretreatment inhibited acetylcholine-induced vasorelaxation. The acetylcholine-induced vasorelaxation is largely mediated by endothelium-derived NO in conduit arteries (9). Effect of NO is mainly mediated by production of cGMP. Thus, we studied the effect of L-DOPA on cGMP. L-DOPA could not reduce relaxation by cGMP, such as membrane permeable cGMP (cpt-cGMP), or soluble guanylate cyclase activator (YC-1), suggesting that the intracellular signaling pathway downstream from cGMP would not contribute this mechanism. Nakatsubo et al. also found that L-DOPA decreased fluorescence levels of diaminofluorescein-2 (DAF-2), a widely used indicator of NO (24). In our preliminary study, L-DOPA decreased nitroprusside-induced fluorescence levels of DAF-2 in the presence of an NO donor in cell-free system (data not shown). This hypothesis is also supported by our data that SOD pretreatment of rings with endothelium induced the subsequent ring relaxation.

L-DOPA is molecularly unstable and can rapidly auto-oxidize in the presence of oxygen or light and oxidize enzymatically to yield free radicals: semi-quinones, O-quinone derivatives and several free radicals such as hydrogen peroxide (H2O2) and superoxide (O2). Rocchitta et al. (25) reported that auto-oxidation of exogenous L-DOPA occurs in vivo in the extracellular compartment of the freely moving rat with a consequent formation of L-DOPA semiquinone (L-DOPA-SQ) in dialysates. NO reacting with superoxide generates peroxyxynitrite (O=NOO) to block NO signaling pathway by inactivating NO (20, 26, 27), leading to decrease of ring relaxation (12, 13). L-DOPA is transported into mammalian cells through the L-type amino acid transporter 1 (LAT1) which is also expressed in vascular endothelium (28). In vitro experiments showed that L-DOPA can lead to accumulation of O2−, and the addition of SOD resulted in higher levels of NO2− (27). In vivo experiment also revealed that SOD can completely inhibit L-DOPA auto-oxidation (20) and decrease spontaneous tone in endothelium-intact rings by scavenging O2− and thereby freeing endothelium-derived NO to relax the blood vessel (29). Therefore, we concluded that L-DOPA mediated inhibition of relaxation is due to inactivation of NO by oxygen free radicals. We do not know whether L-DOPA could produce vasoconstriction via production of reactive oxygen species in vivo, because in vivo endogenous antioxidants, such as ascorbic acid or Vitamin E. Further investigation is needed to clarify in vivo effect of L-DOPA.

MAO-A/B mixed inhibitors may be efficacious in the inhibition of dopamine metabolism and the treatment of PD (30, 32), but there are some side effects of increasing the blood pressure in the presence of a non-selective monoamine oxidase (MAO)-A/B inhibitor or a selective MAO-A inhibitor, L-DOPA increased blood pressure in both PD patients and rats (4, 33). These results indicate that L-DOPA exerts directly on its vasoconstrictive effect without conversion to dopamine.

Minimizing the side effects of hypertension by L-DOPA treatment would be necessary for the maintenance of physical as well as mental well-being of PD patients. The NO-inhibiting effect of L-DOPA on
the vasculature could be applicable to the establishment of a novel therapeutic strategy for the treatment of cardiovascular disorders in PD patients. The concentration of L-DOPA used in the present study (mainly $10^{-5}$ M) is near the plasma concentration in L-DOPA-treated PD patients (approximately $0.5-1.0 \times 10^{-5}$ M) (34). Thus, L-DOPA at this concentration is considered to be enough to inhibit the NO pathway in these patients. From our study, however, in the absence of vasoconstrictors, L-DOPA did not induce contraction of rat aortic rings and the effect of L-DOPA on blood pressure in PD patients was also complex. L-DOPA-mediated inhibition of the NO pathway would result in vasoconstriction when endothelial production of NO was high. However, vasoconstriction due to NO inhibition might be offset by an L-DOPA-mediated sympathetic inhibition. Thus, further studies are needed to clarify the interaction of these different mechanisms on the regulation of the cardiovascular system in PD patients treated with L-DOPA. All together, our experimental results revealed the mechanism about hypertensive effect of L-DOPA and provided a new possibility to the establishment of a novel therapeutic strategy for the treatment of PD patients to avoid side effects (e.g. hypertension) caused by therapy.

REFERENCES


