Diuretic Effects of L-Threo-3,4-Dihydroxyphenylserine (L-Threo-DOPS) in Anesthetized Rats

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Abstract—A synthetic amino acid, L-threo-3,4-dihydroxyphenylserine (L-threo-DOPS), can be converted to (-)-norepinephrine (NE) by aromatic L-amino acid decarboxylase (AADC) in various mammalian tissues. Recent studies have indicated the pressor and diuretic effects of L-threo-DOPS. In this study, we examined the effects of L-threo-DOPS on renal hemodynamics and function in anesthetized rats, and evaluated possible mechanisms of the diuresis. Intravenous infusion of L-threo-DOPS at 120 μg/kg/min exerted a significant increase in mean arterial pressure (MAP). There was a slight but nonsignificant decrease in renal blood flow (RBF). Although the glomerular filtration rate (GFR) remained at a constant level, urine flow (UF) and urinary sodium excretion (U{_sodium}) increased significantly during the drug infusion. Pretreatment with AADC inhibitor, benzerazide, completely blocked both the pressor and diuretic effects of L-threo-DOPS. When the renal perfusion pressure was protected from the pressor effect of the drug by using a Blalock clamp, the drug-induced diuresis was abolished. The diuretic effect of L-threo-DOPS was markedly attenuated by the administration of phentolamine. There was a positive correlation between plasma NE concentration and UF during the infusion of L-threo-DOPS. Intrarenal arterial infusion of L-threo-DOPS at 20 μg/kg/min was without effect on renal function. These results indicate that diuresis and natriuresis induced by L-threo-DOPS are dependent on the pressor effect of NE via peripheral α-adrenoceptor activation.

L-Threo-3,4-dihydroxyphenylserine (L-threo-DOPS) is a synthetic amino acid and can be decarboxylated by aromatic L-amino acid decarboxylase (AADC) to form (-)-norepinephrine (NE) in vitro (1) and in vivo (2). L-Threo-DOPS has been reported to have beneficial effects on akinesia or freezing phenomenon in parkinsonian patients (3) and on orthostatic hypotension in familial amiloid polyneuropathy (4). The hypothermia (5) and ptosis (6) in mice induced by reserpine, an agent which causes both central and peripheral depletion of NE (7), can be reversed by L-threo-DOPS in a dose-dependent manner. Furthermore, L-threo-DOPS produces a slow-onset and long-lasting hypertensive effect in anesthetized rats (8). Thus, this synthetic amino acid appears to be useful as a central and peripheral precursor of NE for various disorders in which noradrenergic transmission is deficient.

Recently, Katsube et al. (9) demonstrated that L-threo-DOPS administered orally in rats and mice produced a dose-dependent diuretic action. They suggested that the diuretic action was mainly due to NE formed by the decarboxylation, based on the findings that the treatment with AADC inhibitors effectively blocked the diuresis. In this study, we examined the effects of L-threo-DOPS on renal hemodynamics and function in anesthetized rats, and we evaluated possible mechanisms of the drug-induced diuresis.
Materials and Methods

Animal preparation
Male Sprague-Dawley rats weighing 300–330 g were anesthetized with sodium pentobarbital (40 mg/kg, i.p.) and placed on a heated surgical tray that maintained rectal temperature between 37°C and 38°C. Supplemental doses of sodium pentobarbital were intravenously infused (30 mg/kg/hr) to maintain a stable state of anesthesia. After tracheotomy, the right femoral vein was cannulated for infusion of physiological saline containing 1.5% inulin. The left carotid artery was also cannulated for blood sampling and for blood pressure measurements. Mean arterial pressure (MAP) was monitored continuously with a pressure transducer (Nihon Kohden AP601G). After an abdominal midline incision was made, the left kidney was exposed, and the renal artery was carefully stripped of connective tissues, followed by the application of 5% phenol in 70% ethanol to exclude the influence of sympathetic nerve activity. In some experiments, a curved 30-gauge needle connected to polyethylene tubing was inserted into the renal artery for intrarenal drug infusion. An electromagnetic flow probe (1.0 mm in diameter) connected to a square-wave flowmeter (Nihon Kohden MFV-2100) was positioned on the renal artery for continuous measurements of renal blood flow (RBF). A polyethylene cannula was inserted into the left ureter for urine collection. The urinary bladder was cannulated to ensure free drainage of urine from the right kidney. At the end of the surgical operation, about 3 ml of physiological saline containing 1.5% inulin was infused slowly to supplement the loss of body fluid and as a priming dose of inulin; this was followed by a sustained infusion of the same solution at a rate of 0.04 ml/min. MAP and RBF were continuously recorded on a polygraph (Nihon Kohden RM 6000). About 1 hr was allowed for stabilization of MAP, RBF and urine flow (UF).

Experimental protocol
Series 1: The experiment consisted of six 20-min clearance periods. After the first control urine collection, L-threo-DOPS (40 μg/kg/min or 120 μg/kg/min) or vehicle (0.9% saline) was infused into the right femoral vein. Ten minutes after the start of the infusion, urine collection was performed during 3 consecutive 20-min periods. Ten minutes after termination of the infusion, another two consecutive 20-min samples were collected as samples of the recovery period. Blood samples (0.2 ml each) were obtained from the left carotid artery at the end of the control, first and third experimental periods, and at the end of the first recovery period. The blood loss was supplemented by an equal volume of 0.9% saline. Plasma was immediately separated by centrifugation.

Series 2: This series of experiments was performed to examine the effects of AADC inhibition on L-threo-DOPS-induced renal actions. Animals were treated with an AADC inhibitor benserazide (50 mg/kg, i.p.) 1 hr prior to the start of the infusion of L-threo-DOPS (120 μg/kg/min).

Series 3: In this series of experiments, the relationship between L-threo-DOPS-induced pressor effects and the renal actions was investigated. During the drug infusion, the left renal perfusion pressure was maintained at a preinfusion level by aortic constriction with a Blalock clamp attached at the aorta just above the origin of the left renal artery. MAP below the clamp was recorded from a catheter inserted into the left renal perfusion pressure. MAP above the clamp was recorded from a catheter inserted into the left carotid artery.

Series 4: In this series of experiments, the effects of the α-adrenoceptor antagonist phentolamine on L-threo-DOPS-induced renal actions were examined. Animals were treated with phentolamine (1 mg/kg, i.v., followed by a continuous infusion of 0.6 mg/kg/hr) 1 hr prior to the start of the infusion of L-threo-DOPS (120 μg/kg/min). α-Adrenergic blockade was verified by the abolishment of the pressor effect of NE (0.5 μg/kg, i.v.).

Series 5: This series of experiments was performed to examine the direct action of L-threo-DOPS on renal function. A nonhypertensive dose of L-threo-DOPS (20 μg/kg/min) was administered directly into the left renal artery.

In Series 2–5, the technique for urine collection and blood sampling was the same as
described for the Series 1 experiments.

**Series 6:** In this series of experiments, L-threo-DOPS and NE concentrations in the plasma were determined after administration of L-threo-DOPS. One hour after the start of the infusion of vehicle or L-threo-DOPS, 3 ml of arterial blood was collected, and plasma was immediately separated.

**Analytical procedures**

Urine and plasma inulin levels were measured by spectrofluorometry (Hitachi 650-60) according to the method of Vurek and Pegram (10). The glomerular filtration rate (GFR) was calculated from the inulin clearance. Sodium and potassium were determined using a flame photometer (Hitachi 205D).

L-Threo-DOPS and NE concentrations in plasma were measured by high performance liquid chromatography (HPLC) with an amperometric detector after extraction by the method of Suzuki et al. (11). Briefly, 1 ml of plasma was mixed with 5 μg of DL-α-methyl-dihydroxyphenylalanine (α-methyl-DOPA, an internal standard for L-threo-DOPS), 5 ng of 3,4-dihydroxybenzylamine (DHBA, an internal standard for NE) and 1 ml of 1 M ammonium phosphate buffer (pH 7.5), and applied to a column of boric acid gel (0.5×5 cm). L-Threo-DOPS and α-methyl-DOPA were eluted with 4 ml of 10% sorbitol solution from the gel, and NE and DHBA were eluted with 2 ml of 1.3 M acetic acid in methanol after washing with 60 ml of distilled water and 2 ml of 0.1 N acetic acid in methanol. The eluate was dried by a stream of N₂ gas, and the residue was dissolved in distilled water. Subsequently, an aliquot of the eluate was injected into an HPLC (Yanaco L-5000) equipped with an amperometric detector (Yanaco VMD-101) and a Yanapac ODS-A column.

**Drugs**

L-Threo-DOPS and benserazide were kindly supplied by Sumitomo Pharmaceuticals Co., Ltd. (Osaka, Japan). Phentolamine hydrochloride was a kind gift from Ciba-Geigy, Ltd. (Takarazuka, Japan). All other chemicals used were of analytical grade.

**Statistical analysis**

All values were expressed as the mean±S.E. For statistical analysis, we used the Kruskal-Wallis nonparametric analysis of variance followed by a Dunnett-type or a Scheffe-type multiple range test for multiple comparisons. In all comparisons, differences were considered significant at P<0.05.

**Results**

**Renal effects of intravenous infusion of L-threo-DOPS:** Intravenous infusion of the vehicle (the time control experiments) had no significant effect on renal hemodynamics and function, although MAP tended to decrease time-dependently during the experiments (from 116±3 in the control period to 107±5 mmHg in the second recovery period). Administration of L-threo-DOPS at 40 μg/kg/min produced a slight increase in MAP, but the changes were not statistically significant compared with the time control experiments. There were no alterations in renal parameters except for slight increases in UF and urinary excretion of sodium (UNaV). When L-threo-DOPS was administered at 120 μg/kg/min, MAP increased significantly from a control value of 117±2 to 137±4 mmHg at 1 hr after the drug infusion. Although slight and non-significant decreases in RBF were observed, there was no change in GFR throughout the experiments. L-Threo-DOPS at this dose produced significant diuretic and natriuretic effects. In the third experimental period, OF and UNaV increased to about 2 and 2.5-fold of each control value, respectively. These effects were recovered gradually after termination of the drug infusion. Urinary excretion of potassium (UKV) did not change throughout the experiments (Fig. 1).

The effects of AADC inhibition on the L-threo-DOPS (120 μg/kg/min)-induced hypertensive and diuretic actions are depicted in Table 1. Treatment with the AADC inhibitor benserazide abolished the increases in MAP. UF and UNaV increased to about 2- and 2.5-fold of each control value, respectively. These effects were recovered gradually after termination of the drug infusion. Urinary excretion of potassium (UKV) did not change throughout the experiments (Fig. 1).

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Fig. 1. Renal hemodynamic and excretory responses to intravenous infusion of L-threo-DOPS. Values are means±S.E. *P<0.05, **P<0.01, compared with the value observed in the time control in the same period. ○, □, Time control (n=9); Δ, L-Threo-DOPS (40 μg/kg/min) (n=6); ●, □□□ L-Threo-DOPS (120 μg/kg/min) (n=9).

The effects of α-adrenergic blockade on the L-threo-DOPS (120 μg/kg/min)–induced hypertensive and diuretic actions are shown in Fig. 3. The α-adrenoceptor antagonist phentolamine attenuated the hypertensive effect induced by L-threo-DOPS, but during L-threo-DOPS infusion MAP remained at a somewhat high level (about 10 mmHg above the control value). Simultaneously, the diuretic effect induced by L-threo-DOPS was markedly attenuated by α-adrenergic blockade, although a slight and nonsignificant increase in UF (about 30%) was observed in the third experimental period. There were no significant changes in UNaV and UKV.

Renal effects of intrarenal arterial infusion of L-threo-DOPS: In order to examine the direct effect of L-threo-DOPS on renal function, an intrarenal arterial infusion of L-threo-DOPS was performed. As shown in Fig. 4, no significant alterations were observed in all the variables. In some rats, L-threo-DOPS
Effects of aortic clamping on renal hemodynamic and excretory responses to intravenous infusion of L-threo-DOPS (120 μg/kg/min). MAP below the clamp (○) was recorded from a catheter inserted into the right femoral artery, and it was used as an index of the left renal perfusion pressure. MAP above the clamp (●) was recorded from a catheter inserted into the left carotid artery. Values are means±S.E. (n=8).

L-Threo-DOPS and NE concentrations in plasma after administration of L-threo-DOPS: Plasma NE concentration in control rats was 0.74±0.12 ng/ml. When L-threo-DOPS was administered intravenously, dose-related increases in plasma NE concentration were observed. When the higher dose, was administered, the NE concentration increased to about 7-fold the control value. However, this increasing effect was significantly attenuated by pretreatment with the AADC inhibitor benzerazide. Plasma L-threo-DOPS concentrations were also elevated following the administration of this drug. Pretreatment with benzerazide produced a further increase in the concentration of L-threo-DOPS (Fig. 5).

Discussion
In the present study, the intravenous infusion of L-threo-DOPS at a higher dose (120 μg/kg/min) produced a pressor effect and a diuretic effect in anesthetized rats. These effects were sustained during the infusion and recovered gradually after cessation of the infusion. To evaluate the possible
Table 1. Renal hemodynamic and excretory responses to intravenous infusion of L-threo-DOPS (120 μg/kg/min) before (−B) and after (+B) benzerazide treatment

|          | MAP (mmHg) | GFR (ml/g-min) | UF (μl/g-min) | U_{Na}V (μEq/g-min) | U_{K}V (μEq/g-min) |
|----------|------------|----------------|--------------|---------------------|--------------------|
|          | −B         | +B             | −B           | +B                  | −B                 | +B                 |
| C        | 117        | 123            | 1.38         | 1.04                | 7.53               | 7.43               | 0.69               | 0.73               | 1.15               | 1.42               |
| ±2       | ±7         | ±0.09          | ±0.07        | ±1.07               | ±0.17              | ±0.13              | ±0.18              | ±0.03              |
| E1       | 131        | 116            | 1.47         | 0.97                | 10.50              | 6.42               | 1.07               | 0.68               | 1.24               | 1.43               |
| ±3       | ±6         | ±0.06          | ±0.06        | ±1.61               | ±0.39              | ±0.17              | ±0.08              | ±0.26              |
| E2       | 135*       | 106            | 1.36         | 1.24                | 16.18*             | 6.80               | 1.66*              | 0.66               | 1.18               | 1.39               |
| ±4       | ±7         | ±0.06          | ±0.10        | ±3.47               | ±1.38              | ±0.40              | ±0.26              | ±0.09              | ±0.29              |
| E3       | 137*       | 104            | 1.37         | 1.14                | 15.97*             | 8.00               | 1.88*              | 0.78               | 1.20               | 1.36               |
| ±4       | ±6         | ±0.09          | ±0.04        | ±3.50               | ±1.79              | ±0.44              | ±0.39              | ±0.02              | ±0.25              |
| R1       | 125        | 102            | 1.18         | 1.04                | 11.21              | 8.25               | 1.41               | 0.82               | 1.02               | 1.36               |
| ±5       | ±5         | ±0.11          | ±0.02        | ±2.21               | ±1.88              | ±0.24              | ±0.46              | ±0.13              | ±0.24              |
| R2       | 118        | 101            | 1.24         | 1.03                | 8.60               | 7.15               | 0.85               | 0.76               | 0.91               | 1.28               |
| ±6       | ±5         | ±0.07          | ±0.01        | ±1.40               | ±1.45              | ±0.19              | ±0.43              | ±0.12              | ±0.20              |

Values are means±S.E. (n=9) *P<0.05, compared with the values observed in the control period.

Fig. 3. Effects of pretreatment with phentolamine on renal hemodynamic and excretory responses to intravenous infusion of L-threo-DOPS (120 μg/kg/min). Values are means±S.E. (n=7).

relationships between the hypertension and the diuresis, the effect of L-threo-DOPS on renal function was also examined under the condition where the rats were protected from the drug-induced pressor action with the aortic clamp. When MAP below the clamp
Fig. 4. Renal hemodynamic and excretory responses to intrarenal arterial infusion of L-threo-DOPS (20 \( \mu \text{g/kg/min} \)). Values are means\( \pm \)S.E. \((n=8)\).

Fig. 5. L-Threo-DOPS (L) and NE (M) concentrations in the plasma after intravenous infusion of L-threo-DOPS. Values are means\( \pm \)S.E. \((n=6)\). **P<0.01, compared with the value observed in the time control. ++P<0.01, compared with the value observed in the L-threo-DOPS (40 \( \mu \text{g/kg/min} \)) administration. *P<0.01, compared with the value observed in the L-threo-DOPS (120 \( \mu \text{g/kg/min} \)) administration.
was maintained at a constant level by con-
stricting the clamp, the diuretic action of L-
theo-DOPS was completely abolished. Under
these conditions, slight decreases in UF and
U_{_{Na,V}} were observed, probably due to the
drug-induced renal vasoconstriction. Thus,
it seems that L-theo-DOPS-induced diuresis
is closely related to the hypertensive effect of
the drug.

Pretreatment with an AADC inhibitor
benserazide also abolished the pressor and
diuretic actions of L-theo-DOPS, thereby
suggesting that NE converted from L-theo-
DOPS is responsible for the above actions.
To confirm this possibility, we determined the
plasma levels of L-theo-DOPS and NE.
Results clearly indicated that plasma NE
levels were increased markedly during L-
theo-DOPS infusion, and the increased levels
were suppressed near the control level by
pretreatment with benserazide. Moreover, a
peripheral $\alpha$-adrenergic blockade with
phentolamine significantly suppressed the
diuretic effect of L-theo-DOPS as well as the
drug-induced hypertensive action. All these
findings lead us to suggest that the diuresis
during the infusion of L-theo-DOPS is due
to the "pressure diuresis" (13) induced by NE
converted from L-theo-DOPS and that the
activation of peripheral $\alpha$-adrenoceptors is
mainly responsible for the hypertensive action.

The pressure diuresis is a well-described
physiological phenomenon in adult animals
(13–16). Several studies (17–20) have pro-
posed a contribution of some physical factor
to such a phenomenon, i.e., the increase in
systemic blood pressure is transmitted to the
peritubular capillaries, and the resultant eleva-
tion of capillary pressure causes a decrease in
water and sodium reabsorption at the proximal
and distal tubules. On the other hand, humoral
factors such as prostaglandins and the renin-
angiotensin system (21, 22) are also reported
to be involved in the pressure diuresis. How-
ever, the precise mechanisms and tubular
sites in which the phenomenon occurs remain
to be determined (13).

In our study, when the $\alpha$-adrenoceptor
antagonist phentolamine was administered,
at a dose which can completely inhibit the
hypertensive action of exogenously applied
NE, the antagonist attenuated markedly but
did not abolish the pressor effect of L-theo-
DOPS. On the other hand, the combination of
phentolamine and the $\beta$-adrenoceptor an-
tagont propranolol inhibited completely the
pressor effect of L-theo-DOPS (data not
shown). These findings indicate that some
factor via $\beta$-adrenoceptor activation partly
contributes to the L-theo-DOPS-induced
hypertension. We observed in some rats that
the infusion of L-theo-DOPS produced an
increase in plasma renin activity, an event
which elevates the level of vasoactive an-
giotensin II. The renin release mechanisms via
$\beta$-adrenoceptor activation is well-established
(23). Thus, NE converted from L-theo-DOPS
may elevate the blood pressure via the stimu-
lation of the renin-angiotensin system. Al-
ternatively, the stimulatory effect on the heart
via $\beta$-adrenoceptor activation may be in-
directly related to L-theo-DOPS-induced
hypertension.

In the present study, the direct action of L-
theo-DOPS on renal function was also in-
vigated. To examine this, an intrarenal
arterial infusion of L-theo-DOPS at a non-
hypertensive dose was carried out, in the
presence or absence of pretreatment with
benserazide. However, the drug infusion was
without effect, thereby indicating that L-
theo-DOPS has no direct action on renal
function.

In conclusion, an intravenous adminis-
tration of L-theo-DOPS produces a hyper-
tensive effect and a diuretic effect in anes-
ethetized rats. The diuretic effect is mainly
due to the "pressure diuresis" via the peripheral
$\alpha$-adrenergic activation induced by NE con-
verted by AADC.

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