Pharmacological effect of Diao-Teng-San, a blended traditional Chinese herb medicine, in spontaneously hypertensive (SHR) and normotensive Wistar-Kyoto (WKY) rats

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(Received May 18, 1987. Accepted July 20, 1987.)

Abstract

We examined the pharmacological effect of Diao-Teng-San (DTS), a blended traditional Chinese herb medicine, on spontaneously hypertensive (SHR) and normotensive Wistar-Kyoto rats (WKY). In response to Diao-Teng-San, systemic blood pressure showed decreases (*i.v.*, *p.o.* and chronic *p.o.*) in a dose-dependent manner in SHRs. In isolated mesenteric arteries from SHRs, norepinephrine-, K^+- and Ca^{2+}-induced contractions were inhibited in a dose-dependent manner. In [^{3}H]nitrendipine binding using crude cardiac and cerebral membranes, the maximal number of binding sites (B_{max}) in the thalamus and hippocampus of SHRs, which were larger than WKYs, were inhibited by DTS, but the apparent dissociation constants (K_d) differed very little. Total and HDL cholesterol values in serum of SHRs were smaller than those of WKYs, but increased by DTS and became close to those of WKYs. β-Lipoprotein, triglyceride and uric acid values in SHRs were increased by DTS. These findings suggest that DTS is involved in lowering blood pressure through α-adrenoceptor blocking and calcium channel antagonistic actions, in inhibiting the increase in the number of calcium channels resembling ones or their components which may play a part in the development and maintenance of high blood pressure, and in improving the functions of the lipid metabolic system in serum.

Key words traditional Chinese herb medicine, Diao-Teng-San (DTS), spontaneously hypertensive rat (SHR), anti-hypertensive action, calcium channel antagonistic action, [^{3}H]-nitrendipine binding, lipid metabolism

Abbreviations DTS, Diao-Teng-San, 釣藤散 ; SHR, spontaneously hypertensive rat ; WKY, Wistar-Kyoto rat

Introduction

Diao-Teng-San (DTS) is a blended traditional Chinese herb medicine (or Kampo medicine), which consists of eleven crude extracts of Gypsum Fibrosum, Auratii Nobilis Pericarpium, Ophiopogonis Tuber, Pinelliae Tuber, Hoelen, Ginseng Radix, Ledebouriellae Radix, Glycyrrhizae Radix, Zingiberis Rhizoma, Uncariae Ramulus et Uncus and Chrysanthemi Flos. It has been reported that DTS has many clinical effects including anti-hypertensive action,[1] anti-gerontal dementia action, anti-headache action and anti-vertigo action.

Recently, the interest in traditional Chinese herb medicine has been revived. Since it has no side effects in terms of typical hypertensive disorders, for instance, bradycardia, tachycardia and orthostatic hypotension, and also is free from harmful adverse effects, DTS has been applied clinically. We[1] reported that DTS was effective for the treatments of patients with not only essential hypertension but also hyperlipemia. But the

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Journal of Medical and Pharmaceutical Society for WAKAN-YAKU 4, 107－115, 1987

mechanism of anti-hypertensive effect of DTS is not yet understood.

This paper discribes further studies on the mechanism of anti-hypertensive action of DTS, namely the effect of DTS on systemic blood pressure, isolated blood vessels, properties of calcium channels in heart and brain and biochemical bindings in serum using spontaneously hypertensive (SHR) and normotensive Wistar-Kyoto rats (WKY).

Materials and Methods

Animals : Male spontaneously hypertensive (SHR) and normotensive Wistar-Kyoto rats (WKY) aged 4 to 16 weeks were used.

Measurement of blood pressure and heart rate : SHRs aged 10 or 11 weeks were anaesthetized with urethane (1.2 g/kg, *s.c.*). The animals were canulated into the left common carotid artery with a polyethylene tube catheter and the systemic blood pressures recorded on an ink-writing oscillograph (RJG-4002, Nihon Kohden Kogyo Co., Japan) through a multiple pressure transducer (MPU-0.5, Nihon Kohden Kogyo Co., Japan). The heart rates were simultaneously recorded through a pulse rate tachometer (RT-5, Nihon Kohden Kogyo Co., Japan) from the pulse wave. Solutions of the drug were injected (*i.v.*) into the right common jugular vein through a polyethylene tube catheter. When the drugs were orally administered to SHR aged 10 weeks (once a day) and 10 to 16 weeks (twice/day) without anaesthetization, the systolic blood pressure and heart rate of the rats were measured by the tail-cuff photoelectric plethysmographic method. Before the measurement, the animals were kept in an air-conditioned chamber at 55℃ for 2 min. When the drugs were chronically administered, the systolic blood pressure was measured 1 hr after each administration of the drug.

Measurement of mechanical reactivity : SHRs aged 10 or 11 weeks were killed by a blow on the occipital region followed by bleeding from the carotid artery, and the anterior mesenteric arteries (outside diameter : 0.3—0.7 mm) were quickly removed and freed of adhering fat and connective tissue. The vessels were cut helically at 45° to the longitudinal axis into strips (about 15×1.5 mm). The helical strips were fixed vertically between hooks in a 50 ml organ bath containing nutrient solution. The responses of the preparations were recorded isometrically on an ink-writing oscillograph (SR-651, Watanabe Inst. Corp., Japan) through a force-displacement transducer (SB-1T-H, Nihon Kohden Kogyo Co., Japan). The resting tension was adjusted to 500 mg. The bathing solution was aerated with a mixture of 95% O_2-5% CO_2 and was maintained at 37±0.5℃.[2] Before the start of experiments, the preparations were allowed to equilibrate in the bathing solution for 60 to 120 min. During the equilibration period, the solution was replaced every 15 to 20 min. The composition of the nutrient solution (Krebs-Henseleit solution) was as follows (mM) : NaCl, 118 ; KCl, 4.96 ; $CaCl_2$, 2.5 ; $NaHCO_3$, 25 ; KH_2PO_4, 1.18 ; $MgSO_4$, 1.18 ; and glucose, 5.55 (pH 7.4).

Studies on relaxation by DTS : Norepinephrine- and high K^+-induced contractions were elicited by addition of 10^{-4} M norepinephrine and 50 mM KCl, respectively, to normal Krebs-Henseleit solution. When the contractions reached a steady state, DTS (10^{-6} g/ml—3×10^{-3} g/ml) was added cumulatively to the bathing fluid. Finally, 10^{-4} M papaverine was added directly to the bathing fluid to fully relax the preparation,[3] and the degree of inhibition of contraction was expressed as 100 %.[2]

Studies on norepinephrine- and K^+-induced contractions : Contractions were elicited by cumulative addition of norepinephrine (10^{-8} M—10^{-4} M) and KCl (0—50 mM) to normal Krebs-Henseleit solution.[4] Maximum contractions of the individual preparations were taken as 100%. DTS was added 10 min before the addition of norepinephrine and KCl.

Studies on Ca^{2+}-induced contractions : Ca^{2+}-induced contractions were elicited by cumulative addition of $CaCl_2$ (10^{-5} M—10^{-2}M) to Ca^{2+}-depleted 54.96 mM K^+-containing Krebs-Henseleit solution, for 10 min after the mesenteric artery strip had been suspended in Ca^{2+}-depleted 1 mM TGTA-

containing Krebs-Henseleit solution for 10 min. $CaCl_2$ was added directly to the bathing fluid.[3,5] Maximum contractions of the individual preparations were taken as 100%. DTS was added 10 min before the addition of $CaCl_2$.

Assay of [^3H] nitrendipine binding : The heart and brain were quickly excised from SHRs and WKYs aged 10 weeks (n = 5, each), and from SHR aged 10 weeks administered (twice/day, *p.o.*) daily with DTS (300 mg/kg, n = 4). Assay of [^{3}H]nitrendipine binding used the procedure published by Ishii *et al.*[6] The properties of [^{3}H]-nitrendipine binding were analyzed by the method of Scatchard.[7]

Measurements of organ weight and biochemical findings : SHRs and WKYs aged 10 to 16 weeks were administred (twice/day, *p.o.*, n=6—8) with DTS or distilled water. The animals aged 16 weeks were anaesthetized with pentobarbitone (30 mg/kg, *i.p.*) and their blood collected from the inferior vena cava through a ventral route. The heart and kidney were quickly removed and weighed. Na^+, K^+, Ca^{2+}, total cholesterol, high density lipoprotein cholesterol (HDL cholesterol), β-lipoprotein, triglyceride, total protein, uric acid, creatinine, blood urea nitrogen (BUN), glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT) and total bilirubin in the serum were measured with an autoanalyzer (736-60E type, Hitachi, Japan).

Drugs : Dried, powdered extract of DTS was obtained by boiling the extract of a mixture composed of Gypsum Fibrosum (5 g), Auratii Nobilis Pericarpium (3 g), Ophiopogonis Tuber (3 g), Pinelliae Tuber (3 g), Hoelen (3 g), Ginseng Radix (2 g), Ledebouriellae Radix (2 g), Glycyrrhizae Radix (1 g), Zingiberis Rhizoma (1 g), Uncariae Ramulus et Uncus (3 g) and Chrysanthemi Flos (2 g) and was supplied by Tsumura Juntendo Co., Japan. The DTS was dissolved in distilled water for use. [^{3}H]Nitrendipine (72.5—79.5 Ci/mmol) was obtained from the Japan Radioisotope Association (New England Nuclear, Tokyo). Nifedipine was supplied by Bayer Yakuhin Co., Ltd., Osaka, Japan. *l*-Norepinephrine bitartrate, papaverine hydrochloride, ethyleneglycol-bis (β-amino-ethyl ether) *N, N, N', N'*-tetraacetic acid (EGTA), Tris-hydroxymethylaminomethane (Tris) and ethylcarbamate (urethane) were obtained from Sigma Chemical Co., U.S.A. Phentobarbitone sodium was obtained from Abbott Laboratories, U.S.A. All other chemicals were of reagent grade.

Other methods : Protein was measured by the method of Lowry *et al.*[8] by using boving serum albumin as a standard. The results were expressed as the mean ± standard error for each group. Significance of the difference was examined by Student's *t*-test.

Results

Effects on blood pressure and heart rate

When DTS at a dose of even 10 mg/kg (n=3) was intravenously administered, blood pressure and heart rate were hardly affected (Fig. 1). At doses of 30 and 100 mg/kg (n=3, each), blood pressure and heart rate showed transient decreases immediately after administration, followed by lowering of the blood pressure in a dose-dependent manner. When SHRs were orally administered (once) with DTS at 300 mg/kg (n=4), blood pressure was shown significantly lower at 23±8.2 and 29±9.0 mmHg after 3 and 5 hr,

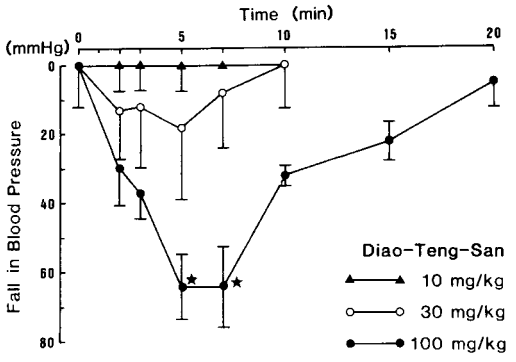

Fig. 1 Effect of Diao-Teng-San (*i.v.*) on systemic blood pressure in SHRs.
The systolic blood pressure of SHRs at pre-administration was 180 to 230 mmHg. Each experiment was performed three times. Points and vertical bars express the mean±S.E. of values. * : $p<0.05$; significantly different from pre-administration values.

respectively, of administration (Fig. 2). At a dose of 30 mg/kg (n=4), blood pressure showed insignificant decreases of 20±10.1 and 20±16.4 mmHg after 3 and 5 hr, respectively. Heart rate showed a significant decrease of 9.7% only at a dose of 300 mg/kg after 3 hr of administration. When SHRs aged 10 to 16 weeks were orally administered (twice/day) with DTS, blood pressure showed significantly lower in a dose-dependent manner (Fig. 3). Blood pressure of the control group (n=6) showed an elevation of approximately 20 mmHg as the animals grew older. When DTS was given at a dose of 3 mg/kg (n=6), there was no elevation in the blood pressure like that in the control group. With a dose of 300 mg/kg (n=6) of DTS, blood pressure at 4 weeks from the start of administration was significantly lower (49 mmHg) than that of the age-matched control group. When administration was withdrawn, blood pressure showed a tendency to return to previous levels. Heart rates differed very little between the DTS and control groups.

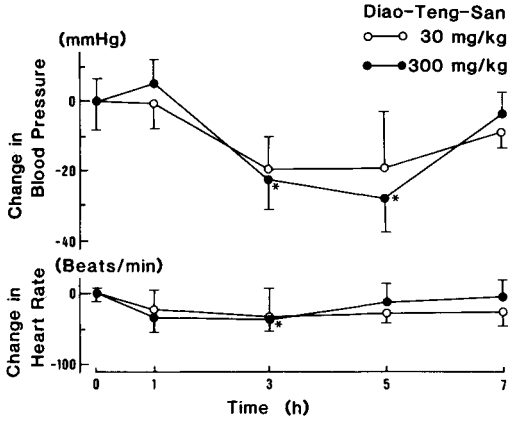

Fig. 2 Effect of Diao-Teng-San (*p.o.*) on systolic blood pressure and heart rate in SHRs.
The systolic blood pressure and heart rate of SHRs at pre-administration were 180—205 mmHg and 372—444 beats/min, respectively. Each experiment was performed four times. Points and vertical bars express the mean±S.E. of values. $*p<0.05$; significantly different from pre-administration values.

Effects on norepinephrine-, K^+- and Ca^{2+}- induced contractions

10^{-4} M Norepinephrine- and 50 mM K^+ -induced contractions were relaxed in a dose-dependent manner by DTS with concentration of 3×10^{-4} g/ml to 3×10^{-3} g/ml (Fig. 4). DTS caused a

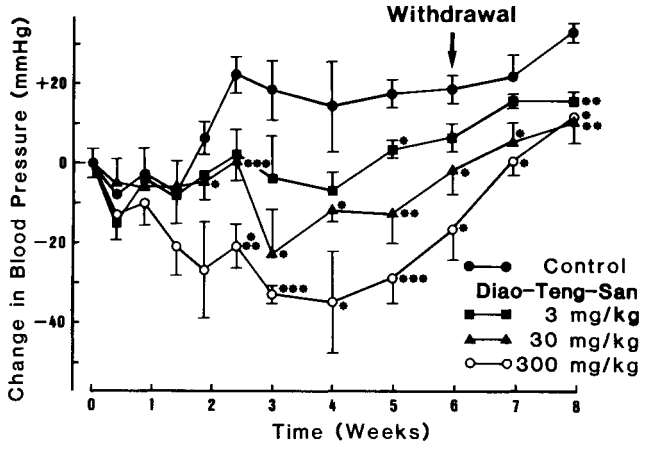

Fig. 3 Effect of Diao-Teng-San (twice/day, *p.o.*) on systolic blood pressure in SHRs.
The systolic blood pressure of SHRs at the start of administration was 200±3.7 mmHg. Each experiment was performed six times. Points and vertical bars express the mean± S.E. of values. * : $p<0.05$, ** : $p<0.01$ and *** : $p<0.001$; significantly different from corresponding control values.

dose-dependent inhibition of norepinephrine-induced contractions, and caused the dose-response curves to shift to the right and downwards (Fig. 5). The ED_{50} values of norepinephrine which induced 50% of maximal contraction by DTS at 3×10^{-5} and 3×10^{-4} g/ml ($4.2\pm0.52\times10^{-7}$ M and $2.1\pm0.43\times10^{-6}$ M, respectively) were significantly higher than those for the control group ($2.8\pm0.15\times10^{-7}$ M). In K^+-induced contractions, DTS at 3×10^{-5} and 3×10^{-4} g/ml caused increase at low concentrations and inhibition at high concentrations of K^+. But DTS at 3×10^{-3} g/ml caused only inhibition of K^+-induced contractions (Fig. 6). In the Ca^{2+}-induced contractions, DTS caused a dose-dependent inhibition and the dose-response curves to shift to the right (Fig. 7). The ED_{50} value of Ca^{2+} which induced 50% of maximal contraction by DTS at 3×10^{-4} g/ml ($2.5\pm0.47\times10^{-3}$ M) was significantly higher than that for the control group ($1.3\pm0.13\times10^{-3}$ M). The inhibitory effect of DTS on norepinephrine-, K^+- and Ca^{2+}-induced contractions was reversible (data not shown).

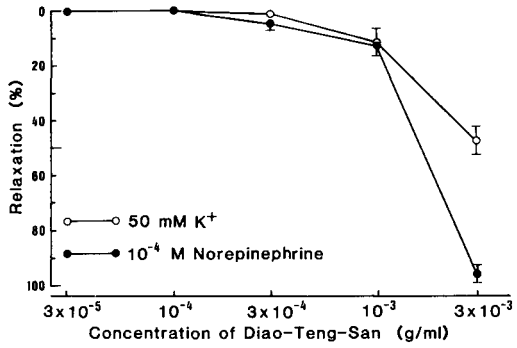

Fig. 4 Dose-response curves for the effect of Diao-Teng-San on norepinephrine- and K^+-induced contractions of isolated SHR mesenteric arteries.
The values for maximum relaxation by 10^{-4} M papaverine in the series with norepinephrine- (n=6) and K^+-induced contractions (n=5) were 297 ± 36.0 and 84 ± 21.8 mg tension, respectively. Points and vertical bars are mean±S.E. of values.

Effects on [^3H]nitrendipine binding

The specific [^{3}H]nitrendipine binding to crude membranes prepared from each region of SHRs

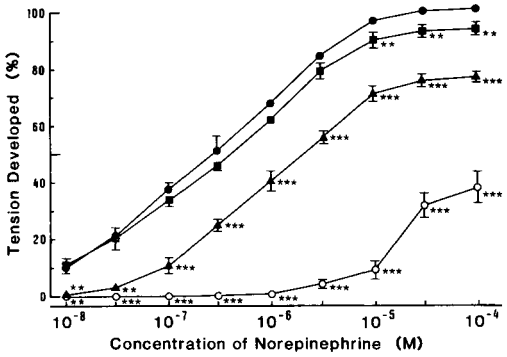

Fig. 5 Dose-response curves for demonstration of the effect of Diao-Teng-San on norepinephrine-induced contraction of isolated SHR mesenteric arteries.
Symbols indicate control values (●, n=12) and values for Diao-Teng-San at 3×10^{-5} g/ml (■, n=6), 3×10^{-4} g/ml (▲, n=6) and 3×10^{-3} g/ml (○, n=6). The value for maximum contraction was 326 ± 21.8 mg tension. Points and vertical bars are mean±S.E. of values. ** : $p<0.01$ and *** : $p<0.001$; significantly different from corresponding control values.

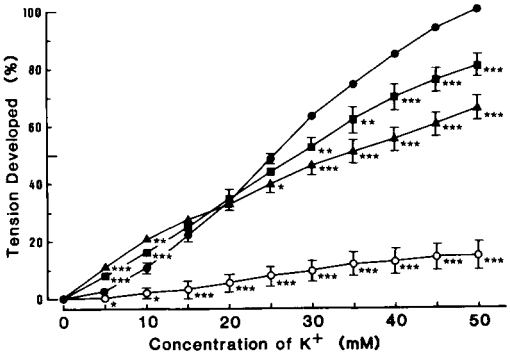

Fig. 6 Dose-response curves for demonstration of the effect of Diao-Teng-San on K^+-induced contraction of isolated SHR mesenteric arteries.
Symbols indicate control values (●, n=14) and values for Diao-Teng-San at 3×10^{-5} g/ml (■, n=7), 3×10^{-4} g/ml (▲, n=7) and 3×10^{-3} g/ml (○, n=7). The value for maximum contraction was 213 ± 8.4 mg tension. Points and vertical bars are mean±S.E. of values. * : $p<0.05$, ** : $p<0.01$ and *** : $p<0.001$; significantly different from corresponding control values.

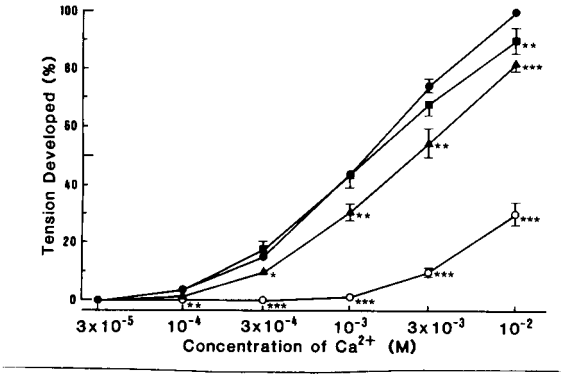

Fig. 7 Dose-response curves for demonstration of the effect of Diao-Teng-San on Ca^{2+}-induced contraction of isolated SHR mesenteric arteries.

Symbols indicate control values (●, n=10) and values for Diao-Teng-San at 3×10^{-5} g/ml (■, n=5), 3×10^{-4} g/ml (▲, n=5) and 3×10^{-3} g/ml (○, n=5). The value for maximum contraction was 122±12.0 mg tension. Points and vertical bars are mean±S.E. of values. * : $p<0.05$, ** : $p<0.01$ and *** : $p<0.001$; significantly different from corresponding control values.

and WKYs was saturated monophasically with high affinity (data not shown).

The properties of [^{3}H]nitrendipine binding of the tissues of DTS-treated SHRs were compared with age-matched untreated SHRs or WKYs. In the hypothalamic, thalamic and hippocampal membranes, the maximal numbers of binding sites (B_{max}) for the DTS-treated SHR group were significantly lower (10.9, 37.8 and 43.0%, respectively) than those of the untreated SHR group (Fig. 8). In the striatal membranes, B_{max} values for the DTS-treated SHR group were lower, but not significantly, than those for the untreated SHR group. In the hippocampal membranes, B_{max} values for the DTS-treated SHR group were significantly lower (30.8%) than those for the WKY group. The apparent dissociation constants (K_d) for the DTS-treated SHR group differed very little from those for the brain regions of untreated SHR or WKY groups. In the cardiac membranes, K_d and B_{max} values for the DTS-treated SHR group differed very little from those

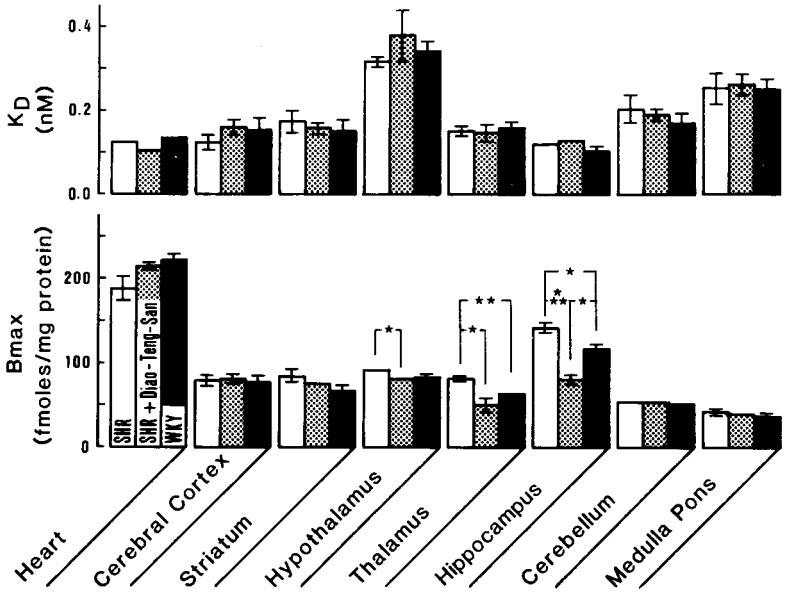

Fig. 8 Properties of [^{3}H]nitrendipine binding to cardiac and cerebral membranes from SHRs and WKYs, and from SHR treated with Diao-Teng-San.

The experiments were performed four to five times. Columns and vertical bars express the mean±S.E. of values. * : $p<0.05$, ** : $p<0.01$, and *** : $p<0.001$; significantly different from corresponding SHR or WKY values.

Table I Effect of Diao-teng-San on body and organ weights and biochemical serum findings in SHRs or WKYs aged 16 weeks.

		SHR				WKY
		control	Diao-Teng-San 3 mg/kg	Diao-Teng-San 30 mg/kg	Diao-Teng-San 300 mg/kg	
Body weight	(g)	224±14.4	289±7.5^{c,f}	303±7.0^{c}	310±5.4^{c,e}	336±5.6^{b}
Heart	(g/100g BW)	0.42±0.003	0.40±0.007^{a,f}	0.41±0.016^{f}	0.38±0.006^{c,f}	0.29±0.005^{c}
Kidney	(g/100g BW)	0.77±0.020	0.67±0.019^{b}	0.70±0.013^{a}	0.72±0.007^{a,d}	0.69±0.007^{b}
Na^+	(mEq/l)	144±0.2	145±0.6^{b,d}	143±0.3^{a}	144±0.4	143±0.4^{a}
K^+	(mEq/l)	4.7±0.04	4.9±0.09^{f}	5.1±0.06^{c,f}	5.0±0.07^{b,f}	4.1±0.09^{c}
Ca^{2+}	(mEq/l)	4.9±0.05	4.8±0.10^{e}	4.8±0.07^{e}	4.8±0.03^{f}	5.2±0.06^{b}
Total cholesterol	(mg/dl)	41±2.3	54±2.8^{b,f}	52±0.8^{c,f}	48±1.2^{a,f}	105±4.3^{c}
HDL cholesterol	(mg/dl)	27±1.5	34±2.2^{a,f}	37±2.3^{b,f}	31±1.0^{a,f}	65±2.4^{c}
β-Lipoprotein	(mg/dl)	49±5.4	66±12.6	64±14.1	106±10.6^{c,f}	50±4.4
Triglyceride	(mg/dl)	54±6.9	59±6.0	64±7.1	99±8.7^{c,e}	62±3.6
Total protein	(g/dl)	6.2±0.11	6.5±0.14^{f}	6.2±0.15^{d}	6.1±0.09^{d}	5.8±0.05^{a}
Uric acid	(mg/dl)	1.7±0.07	2.8±0.33^{b,d}	2.6±0.19^{c,f}	1.9±0.13^{d}	1.2±0.28
Creatinine	(mg/dl)	0.7±0.01	0.8±0.03^{b,f}	0.7±0.02^{d}	0.7±0.02^{e}	0.6±0.03^{b}
BUN	(mg/dl)	20±0.7	23±1.4^{e}	22±1.0^{f}	20±0.9^{d}	17±0.6^{b}
GOT	(Karmen-U)	148±11.9	198±9.8^{b,f}	184±9.8^{a,f}	147±3.7^{f}	69±6.8^{c}
GPT	(Karmen-U)	51±5.7	43±3.0^{f}	37±3.0^{f}	31±1.6^{b,f}	17±0.5^{c}
Total bilirubin	(mg/dl)	0.2±0.03	0.2±0.02^{e}	0.2±0.02^{e}	0.3±0.02^{b}	0.3±0.03^{a}

The values are expressed as the mean±S.E. for 6 to 8 rats.
^{a} : $p<0.05$, ^{b} : $p<0.01$ and ^{c} : $p<0.001$; significantly different from corresponding control SHR values.
^{d} : $p<0.05$, ^{e} : $p<0.01$ and ^{f} : $p<0.001$; significantly different from corresponding WKY values.

for untreated SHR or WKY groups.

Effects on body and organ weights and biochemical findings in serum

The effect of DTS on body and organ weight and biochemical findings in serum is summarized in Table I. Body weight of the DTS-treated group showed significant increases in a dose-dependent manner over that of the untreated SHR group and was significantly lower than that of the WKY group. The heart and kidney weights of the DTS-treated group showed significant decreases over those of the untreated SHR group.

Na^+ and Ca^{2+} values of the DTS-treated group differed little from those for the untreated SHR group, but K^+ values showed significant increases.

Total and HDL cholesterol values of the untreated SHR group showed significantly lower than those of the WKY group. Total cholesterol, HDL cholesterol, β-lipoprotein, triglyceride, total protein and uric acid values of the DTS-treated group showed increases over those for the untreated SHR group. BUN, GOT and GPT values for the DTS-treated group differed very little from those for the untreated SHR group.

Discussion

Since the intravenous administration of DTS in SHRs was shown to lower the systemic blood pressure in a dose-dependent manner (Fig. 1), it may have an anti-hypertensive action with itself but not its metabolites. Oral administration of DTS at doses of 30 and 300 mg/kg slowly and continuously lowered the systolic blood pressure from 20 to 29 mmHg after 3 to 5 hr (Fig. 2). Furthermore, chronic oral administration (twice/day) of DTS in SHRs lowered the systolic blood pressure in a dose-dependent manner (Fig. 3), but did not show any effect on the heart rate. In SHRs in a continuous hypertensive stage from 10 to 16 weeks-old, therefore, DTS has an anti-hypertensive action but does not affect the heart rate. On the other hand, Ozaki *et al*.[9] reported that DTS in stroke-prone SHRs (SHR-SP) caused only a minor reduction in the blood pressure.

These differences may suggest that for SHR-SP, which is a model animal of malignant hypertension, it is difficult to lower the systemic blood pressure.

In isolated mesenteric arteries from SHRs, DTS relaxed 10^{-4} M norepinephrine-induced contraction and shifted the dose-response curves for norepinephrine-induced contraction to the right and downwards (Figs. 4 and 5). DTS at high concentrations also relaxed 50 mM K^+-induced contraction and inhibited K^+-induced contraction (Figs. 4 and 6). Furthermore, DTS shifted the dose-response curves for Ca^{2+}-induced contraction to the right (Fig. 7). High K^+-induced contraction resulted from increases in Ca^{2+} influx through activation of voltage-sensitive calcium channels (opening or widening) of the muscle cell membrane.[10,11] On the other hand, because of cumulative addition of Ca^{2+}-induced contraction of isolated arteries in Ca^{2+}-depleted K^+-depolarizing solution after treatment with EGTA-containing Ca^{2+}-depleted solution, it is possible that the Ca^{2+}-induced contraction depends on the influx of Ca^{2+} into the vascular smooth muscle cells from the external medium.[12] Accordingly, all these results support at least the idea that DTS may antagonize α-adrenoceptor and transmembrane influx of Ca^{2+}, as well as calcium channel antagonists,[12] and anti-hypertensive effect of DTS may play a part in peripheral vasodilating action.

Belleman *et al*.,[13] Murphy and Snyder[14] and Ehlert *et al.*[15] have shown that, of the 1,4-dihydropyridine derivatives, [^{3}H]nitrendipine binds specifically to membrane fractions of the brain and heart and to homogenate preparations of the longitudinal muscle of the ileum. [^{3}H]Nitrendipine binding assay proved to be very useful for the study of calcium channels.[16] Ishii *et al.*[6] reported that the B_{max} of [^{3}H]nitrendipine binding in the striatum, thalamus and hippocampus for SHRs showed increases over those in WKYs, but the K_d differed very little between WKYs and SHRs at 4, 6, 10 and 15 weeks of age. These increased number of [^{3}H]nitrendipine binding sites, reflected in calcium channels resembling voltage-sensitive ones or their components of SHR, may play a part in the development and maintenace of high blood pressure. When DTS was chronically administered to SHRs, the B_{max} in the striatum, thalamus and hippocampus of the brain was lowered either insignificantly or significantly as compared with untreated SHRs (Fig. 8). These values were also lowered by chronically administered nifedipine and nimodipine (50 mg/kg, each) but not by phentolamine and propranolol (20 and 10 mg/kg, *p.o.*, respectively) (unpublished data). Panza *et al.*[17] reported that chronic treatment of mice with verapamil or nifedipine has been shown to decrease binding of [^{3}H]nitrendipine to neuronal membranes. These data suggest that DTS may act on the calcium channels of the central nervous system either directly or as a calcium channel antagonist, and may increase the cerebral blood flow. This phenomenon may play a part in anti-hypertensive effect through the central nervous system in SHRs.

DTS was shown to increase body weight and decrease enlargement of the heart and kidney in SHRs (Table I). In biochemical serum findings, DTS caused increasing of the decreases in total and HDL cholesterol values of SHRs in comparison with WKYs and also increased β-lipoprotein, trigriceride and uric acid in SHRs. These results suggest that DTS improves abnormal lipid metabolic system in SHRs. On the other hand, we[1] reported that in typical hypertension patients, DTS significantly decreased total serum cholesterol at the high pre-remedy levels, significantly decreased triglyceride at normal and high pre-remedy levels and significantly increased HDL cholesterol in all cases, but DTS did not affect any significant changes in Na^+ and K^+ levels. Therefore, DTS may have less effect on serum Na^+, K^+ and Ca^{2+} levels, but these differences between SHRs and human patients on the mechanism of lipid metabolic system are not known.

Conclusion

In SHRs, DTS may lower the blood pressure, inhibit an increase in the number of [^{3}H]nitrendipine binding sites in the striatum, thalamus and

hippocampus and improve the functions of the lipid metabolic system.

Acknowledgements

We are grateful to Tsumura Juntendo Co. (Japan) for the generous gift of Diao-Teng-San.

和文抄録

高血圧自然発症（SHR）および正常血圧Wistar-Kyoto（WKY）ラットを用いて釣藤散（DTS）の薬理学的効果を調べた。DTSにより，SHRの全身血圧は，用量依存性の下降（静脈内，経口および慢性経口投与）を認めた。SHRから摘出した腸間膜動脈では，norepinephrine, K^+ および Ca^{2+} による収縮を用量依存性に抑制した。心臓および脳粗膜標品を用いた〔^{3}H〕nitrendipine結合では，WKYに比較してSHRの視床および海馬における最大結合量（B_{max}）は増加しているが，DTSにより抑制された。解離定数（K_d）にはほとんど影響は見られなかった。血清生化学的検査において，SHRの総コレステロールおよびHDL-コレステロール値はWKYに比べて低値を示すが、DTSにより増大した。更にβ-リポタンパク，トリグリセライドおよび尿酸値が増大した。これらのことから，DTSは，α-アドレナリン受容体遮断作用およびカルシウム・チャンネル拮抗作用を介した血圧下降作用，高血圧の発症・持続に関与すると思われるカルシウム・チャンネルまたはその構成成分の数の増加抑制作用，更に，血清脂質代謝系の機能を改善する作用を持つと考えられる。

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