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Effects of dicentrine on haemodynamic, plasma lipid, lipoprotein level and vascular reactivity in hyperlipidaemic rats

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1 The effects of dicentrine on haemodynamic, plasma lipid, lipoprotein level and vascular reactivity were investigated in Wistar-Kyoto (WKY) and spontaneously hypertensive (SH) rats, fed a high fat-high cholesterol diet.

2 In high fat-high cholesterol (HF-HC) diet fed WKY and SH rats, oral administration of dicentrine (5 and 10 mg kg^{-1}, twice a day) for 4 weeks caused significant reductions in total plasma cholesterol (CE) by reducing the low density lipoprotein (LDL) fraction, and reductions in total plasma triglyceride (TG) by reducing the very low density lipoprotein (VLDL) fraction.

3 Dicentrine therapy was associated with increased high density lipoprotein (HDL)-cholesterol levels; thus the ratio of total plasma cholesterol to HDL-cholesterol was improved.

4 In HF-HC diet fed conscious WKY and SH rats, oral administration of dicentrine (5 and 10 mg kg^{-1}, twice a day) also evoked dose-related decreases in mean arterial pressure (MAP) which were of greater magnitude in SH rats. Neither dose of dicentrine caused a significant change in heart rate (HR).

5 The aortic arches from SH rats fed the HF-HC diet for 8 weeks were significantly more affected by the atherosclerotic lesions than the abdominal aortae and renal arteries of WKY and SH rats. Oral administration of dicentrine (5 and 10 mg kg^{-1}) for 4 weeks did not diminish the atherosclerotic lesion areas in WKY and SH rats.

6 In aortae of the hyperlipidaemic rats, significantly attenuated EC_{50} values and augmented maximal responses for phenylephrine-induced contraction were obtained. Endothelium-dependent relaxation to acetylcholine was abolished, while endothelium-independent relaxation to nitroprusside was well preserved. Dicentrine therapy caused significantly augmented EC_{50} values and attenuated maximal responses for phenylephrine-induced contraction in hyperlipidaemic rats. However, dicentrine neither prevented the impaired relaxation to acetylcholine, nor affected the relaxation to nitroprusside during atherosclerosis progression.

7 It is concluded that dicentrine decreases MAP, plasma CE, LDL-CE, plasma TG, VLDL-TG, vascular hyperreactivity to phenylephrine and increases HDL-CE levels. Dicentrine may thus hold potential for the reduction of two of the major risk factors, hypertension and hyperlipidaemia, for cardiovascular disease.

Keywords: Dicentrine; lipid; lipoprotein; mean arterial pressure; vascular reactivity; hyperlipidaemia

Introduction

Hypertension and abnormal plasma lipid levels are two of the major risk factors for cardiovascular diseases. Traditional antihypertensive therapy with β-adrenoceptor blockers or diuretics is now known to affect adversely the plasma lipid profile (Weinberger, 1986; William *et al.*, 1989). Several long-term prospective clinical studies have implicated these changes in plasma lipids as a significant factor in the failure of antihypertensive therapy to reduce the incidence of ischaemia heart diseases and related mortality (William *et al.*, 1989). Recent data demonstrate that α- and β-adrenoceptor blockade can influence lipid metabolism, suggesting that sympathetic activity may play a role in lipid metabolism. Preliminary studies suggest that α-blockade may decrease total plasma cholesterol (CE), low density lipoprotein (LDL)-cholesterol, triglyceride (TG) and increase high density lipoprotein (HDL)-cholesterol (Miller, 1987).

Recently, we found that dicentrine, an aporphine derivative isolated from the plant *Lindera megaphylla*, possessed α_1-adrenoceptor antagonistic action in isolated vessels (Teng *et al.*, 1991) and antihypertensive effect in spontaneously hypertensive (SH) rats (Yu *et al.*, 1992). In this study, we have evaluated the effects of dicentrine on haemodynamic, plasma lipid, lipoprotein and vascular reactivity in SH and WKY rats fed with high fat-high cholesterol (HF-HC) diet.

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Methods

Rat model of hyperlipidaemia

Male SH rats weighing 230–250 g (Charles River Breeding Laboratories, Wilmington, MA, U.S.A.) (mean arterial pressure (MAP): 160 ± 9 mmHg; heart rate (HR): 365 ± 12 beats min^{-1}) and age-matched WKY control animals weighing 230–260 g (Biological Research Laboratories, Fullinsdorf, Switzerland) (MAP: 102 ± 4 mmHg; HR: 357 ± 9 beats min^{-1}) were used in this study. The rats were housed in their own cages and given food (as follows) and water *ad libitum*. WKY and SH rats were fed either normal rat chow (No. 5001, Ralston Purina, St. Louis, MO, U.S.A.) or chow supplemented with 20% olive oil and 1% cholesterol (HF-HC diet) for 8 weeks prior to the study and during the dicentrine treatment period. No significant difference in food intake (g/day) was observed among the normal chow, HF-HC chow and dicentrine-treated groups. Since the 1% cholesterol and 20% olive oil diets produce a relatively mild hyperlipidaemia

in the rat (DeLamatre & Roheim, 1981; Krause & Newton, 1985), we added the additional bile acid to increase cholesterol absorption so that we might obtain more marked differences in plasma cholesterol between groups.

The rats were randomly assigned to one of the three following treatment groups: controls, HF-HC chow and dicentrine (5 and 10 mg kg^{-1}, orally, twice a day)/HF-HC chow. At the end of the period of receiving the HF-HC chow and dicentrine treatment/HF-HC chow, the rats MAP and HR were monitored with an electronic analyzer. Rats were anaesthetized with sodium pentobarbitone (30 mg kg^{-1}, i.p.), a blood sample was obtained for determination of lipoprotein analysis after 16 h overnight fast, and then the rats were killed and various vessels (aortic arch, abdominal aorta and renal artery) were removed.

Measurement of plasma lipids and lipoproteins

Plasma lipoproteins were separated by a one-step density gradient ultracentrifugation technique (Demacker *et al.*, 1983). The very low density lipoprotein (VLDL), low density lipoprotein (LDL), high density lipoprotein (HDL) fractions correspond to the density intervals < 1.006 g ml^{-1}, 1.006–1.063 g ml^{-1} and 1.063–1.21 g ml^{-1} respectively. Total plasma cholesterol and the cholesterol concentrations in each lipoprotein fraction were assayed by an enzymatic colorimetric technique with Boehringer Mannheim GmbH diagnostic kits (Roschlau *et al.*, 1974) and triglycerides were measured with Biomerieux kits (Takayama *et al.*, 1977). Apolipoprotein quantitation was performed with the radial immunodiffusion assay described by Chong *et al.* (1987).

Histological examinations

Segments of the three arteries obtained from control and hyperlipidaemic rats, were opened longitudinally and stained with $AgNO_3$. Briefly, the opened segments were mounted on pieces of cork and stained in the dark with $AgNO_3$ (24 mM) in the presence of glucose (233 mM) and HEPES buffer (20 mM) at pH 7.4 for 60 s. After being rinsed with glucose solution, the tissues were fixed with 2.5% glutaraldehyde in 0.1 M sodium cacodylate buffer. The fixed tissues were dehydrated, embedded in DPX, and their luminal surface was examined by light microscopy.

Segments of the three arteries were opened longitudinally and put into 2.5% glutaraldehyde for fixation. After fixation for at least 8 h, the specimen was dehydrated in 50, 60, 70, 80, 90 and 95% alcohol orderly for 20 min in each concentration. Then, it was put in amyl acetate for 10 min and critical point drying was carried out with liquid carbon dioxide. The specimen was coated with gold and was observed under scanning electron microscope (sEM, JXA-840, JEOL, Japan).

Pharmacological measurements

Rats were anaesthetized with sodium pentobarbitone, and aortic arches or abdominal aortae were isolated and cleaned of surrounding tissue. Aortic rings of about 3 mm in length and mounted in organ baths containing 5 ml Krebs solution (composition mM: NaCl 118, KCl 4.0, $CaCl_2$ 1.9, $MgSO_4$ 1.2, $NaHPO_4$ 1.2, $NaHCO_3$ 25 and glucose 11.7) and equilibrated at 37°C with 95% O_2:5% CO_2 gas mixture. Two stainless steel hooks were inserted into the aortic wall, one was fixed while the other was connected to a transducer. Aortae were equilibrated in the medium for 60 min with three changes of Krebs solution and maintained under an optimal tension of 1 g before specific experimental protocols were initiated. Contractions were recorded isometrically via a force-displacement transducer connected to a Grass polygraph. The cumulative concentration-response curve was obtained with phenylephrine (0.01–30 μM) for 24 min at 3 min intervals. Aortic rings were contracted with 3 μM phenylephrine for 15 min and then subsequently relaxed by the cumulative addition of acetylcholine or nitroprusside. In some experiments, the endothelium was removed mechanically by rubbing the intimal surface with filter paper moistened with the buffer. Relaxation values were expressed as percentage decreases of the phenylephrine (3 μM)-induced contraction.

Data analysis

The experimental results are expressed as the mean ± s.e. mean and accompanied by the number of observations. Statistical significance was assessed by Student's t test and P values less than 0.05 were considered significant.

Drugs

(+)-Dicentrine was prepared according to the method described previously by Chen *et al.* (1991). The following drugs were used: phenylephrine, acetylcholine, nitroprusside, cholesterol and bile acid, all obtained from Sigma Chemical Co. (St. Louis, MO, U.S.A.). Dicentrine was suspended in arabic gum and distilled water. Control rats were given 1 ml kg^{-1} of the vehicle.

Results

Plasma lipid and lipoprotein profiles

The plasma lipid and lipoprotein profiles of WKY and SH rats fed either normal or high fat-high cholesterol (HF-HC) chow are summarized in Table 1. Total plasma CE, VLDL-, LDL-CE, total plasma TG, VLDL-, LDL- and HDL-TG levels were markedly elevated in HF-HC chow fed groups compared with the normal chow fed rats. However, the HDL-CE was decreased in HF-HC chow rats (Table 1). The increases of plasma CE and TG levels were time-dependent (Figure 1). The increase in total plasma CE appeared generally to plateau out whereas the TG level appeared to increase over the whole time period of the study. Although the data also showed that higher levels of CE and TG were achieved in SH rats than in WKY rats, there were no statistical differences.

Table 1 Plasma lipid and lipoprotein profiles of WKY and SH rats treated with either normal or high fat-high cholesterol chow

		Cholesterol (mg dl^{-1})					*Triglyceride* (mg dl^{-1})			
Rat		*Total*	*VLDL*	*LDL*	*HDL*	*CE/HDL*	*Total*	*VLDL*	*LDL*	*HDL*
WKY	Normal chow	55 ± 1	8 ± 2	28 ± 2	17 ± 1	3.23 ± 0.8	114 ± 14	91 ± 4	12 ± 4	8 ± 3
	HF-HC chow	218 ± 6**	38 ± 2**	170 ± 4**	9 ± 1**	24.22 ± 2	231 ± 10**	180 ± 8**	22 ± 5	26 ± 2**
SH	Normal chow	60 ± 1	9 ± 2	36 ± 2	19 ± 3	3.16 ± 0.5	97 ± 6	76 ± 3	9 ± 2	12 ± 1
	HF-HC chow	244 ± 3**	40 ± 1**	195 ± 3**	9 ± 1*	27.11 ± 2	271 ± 12**	200 ± 5**	35 ± 7*	30 ± 4**

Values are means ± s.e. mean for n observations ($n = 9$). VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; HF-HC, high fat-high cholesterol.
*$P < 0.01$ and **$P < 0.001$ denote significant differences between normal and HF-HC chow values in each compared group of WKY or SH rats.

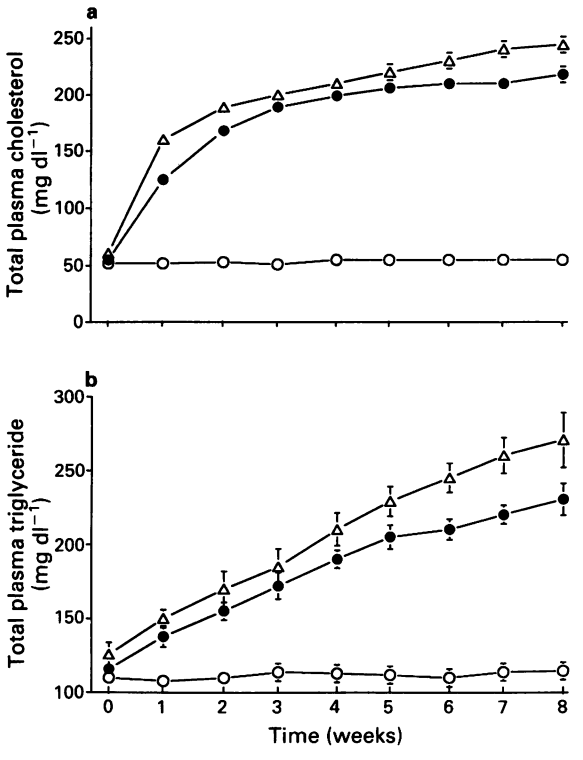

Figure 1 Total plasma cholesterol (a) and triglyceride (b) levels of normal chow fed rats (○), HF-HC chow fed rat (WKY ●, SH rats △) during experimental periods. Each point represents the mean and vertical bars show s.e. mean ($n = 15-20$).

Effects of dicentrine on haemodynamic, plasma lipid and lipoprotein profiles in hyperlipidaemia rats

Oral administration of dicentrine (5 and 10 mg kg^{-1}, twice a day) for 4 weeks affected plasma lipid, lipoprotein levels and as well as mean arterial pressure (MAP) in WKY and SH rats treated with HF-HC chow (Table 2). Dicentrine evoked a dose-related hypotensive effect, which was of greater magnitude in SH rats (5 mg vs 10 mg kg^{-1} of dicentrine-evoked hypotensive effect was not statistically different in WKY groups, whereas $P<0.01$ in SH groups). A higher dose of dicentrine (10 mg kg^{-1}) did not cause significant changes in heart rate (HR) of WKY and SH rats (Table 2). Both in WKY and SH rats receiving the HF-HC diet, dicentrine caused dose-dependent reductions in total plasma CE by reducing the LDL fraction, and reductions in total plasma TG by reducing VLDL fraction (Figure 2). Dicentrine treatment was associated with increased HDL-CE levels, thus the ratio of total plasma CE to HDL-CE was improved (Figure 3).

Histological examination of the intimal surface of the hyperlipidaemic arteries

No visible atherosclerotic lesions were detected in any vessels removed from control rats. Light microscopic study of vessels from HF-HC fed WKY and SH rats indicated that the aortic arch had grossly visible dots of lipid deposition. The thickness of the fatty streaks significantly augmented with the time rats were fed the HF-HC diet (data not shown). The aortic arches from SH and WKY rats fed the HF-HC diet for 8 weeks were significantly more affected by the atherosclerotic lesions than the abdominal aortae and renal arteries of WKY and SH rats. However, the lesions of aortic arches of SH rats were more severe than in WKY rats fed with the same HF-HC diet.

Effects of dicentrine on the vascular reactivity in hyperlipidaemic rats

Increasing concentrations of phenylephrine (0.01–30 μM) evoked concentration-dependent contraction in control segments of the aortic arch and abdominal aorta (Figure 4). Both in the aortic arch and abdominal aorta of WKY and SH rats fed HF-HC diet for 8 weeks, significantly attenuated EC_{50} values and augmented maximal responses for phenylephrine were obtained (Table 3, Figure 4). Oral administration of dicentrine (5 and 10 mg kg^{-1}, twice a day) for 4 weeks, inhibited the contraction caused by phenylephrine in a concentration-dependent manner in aortic arch and abdominal aorta of hyperlipidaemic rats (Figure 4). Dicentrine (5 and 10 mg kg^{-1}) caused significantly augmented EC_{50} values and attenuated maximal responses for phenylephrine-induced contraction in hyperlipidaemic WKY and SH rats. In SH rats, the augmented EC_{50} values and attenuated maximal responses of phenylephrine caused by dicentrine were more pronounced than in WKY (Table 3).

During contractions caused by phenylephrine (3 μM) for 15 min, cumulative addition of acetylcholine (0.01–30 μM) evoked concentration-dependent relaxation in control segments of the aortic arch and abdominal aorta (Figure 5). However, whilst the concentration-dependent relaxation to acetylcholine was significantly attenuated, that to nitroprusside was unaffected in hyperlipidaemic WKY and SH rats (Table 3, Figure 5). Oral administration of dicentrine (5 and 10 mg kg^{-1}) for 4 weeks, neither prevented the impaired relaxation to acetylcholine, nor affected the relaxation to nitroprusside in hyperlipidaemic rats (Figure 5).

Table 2 Effects of dicentrine on haemodynamic, plasma lipid, lipoprotein and glucose levels in WKY and SH rats treated with high fat-high cholesterol chow

	WKY			*SH rats*		
	Control	*Dicentrine*		*Control*	*Dicentrine*	
		5 mg kg^{-1}	10 mg kg^{-1}		5 mg kg^{-1}	10 mg kg^{-1}
MAP (mmHg)	100 ± 3	87 ± 2**	81 ± 4***	160 ± 3	119 ± 5***	102 ± 3***
HR (beats min^{-1})	357 ± 9	349 ± 11	347 ± 12	365 ± 14	358 ± 10	356 ± 14
CE (mg dl^{-1})	218 ± 6	166 ± 6***	94 ± 4***	244 ± 3	146 ± 5***	79 ± 6***
TG (mg dl^{-1})	231 ± 10	142 ± 12***	122 ± 10***	271 ± 12	136 ± 18***	110 ± 10***
Apo-B (mg dl^{-1})	20 ± 3	15 ± 2	10 ± 1**	23 ± 4	13 ± 2*	9 ± 3**
Glucose (mg dl^{-1})	142 ± 11	143 ± 7	144 ± 8	136 ± 8	140 ± 5	147 ± 5

Values are means ± s.e. mean for n observations ($n = 9-15$). MAP, mean arterial pressure (mmHg); HR, heart rate (beats min^{-1}); CE, cholesterol (mg dl^{-1}); TG, triglyceride (mg dl^{-1}); Apo-B, apolipoprotein B (mg dl^{-1}).
*$P<0.05$; **$P<0.01$ and ***$P<0.001$ denote significantly different from the respective control values.

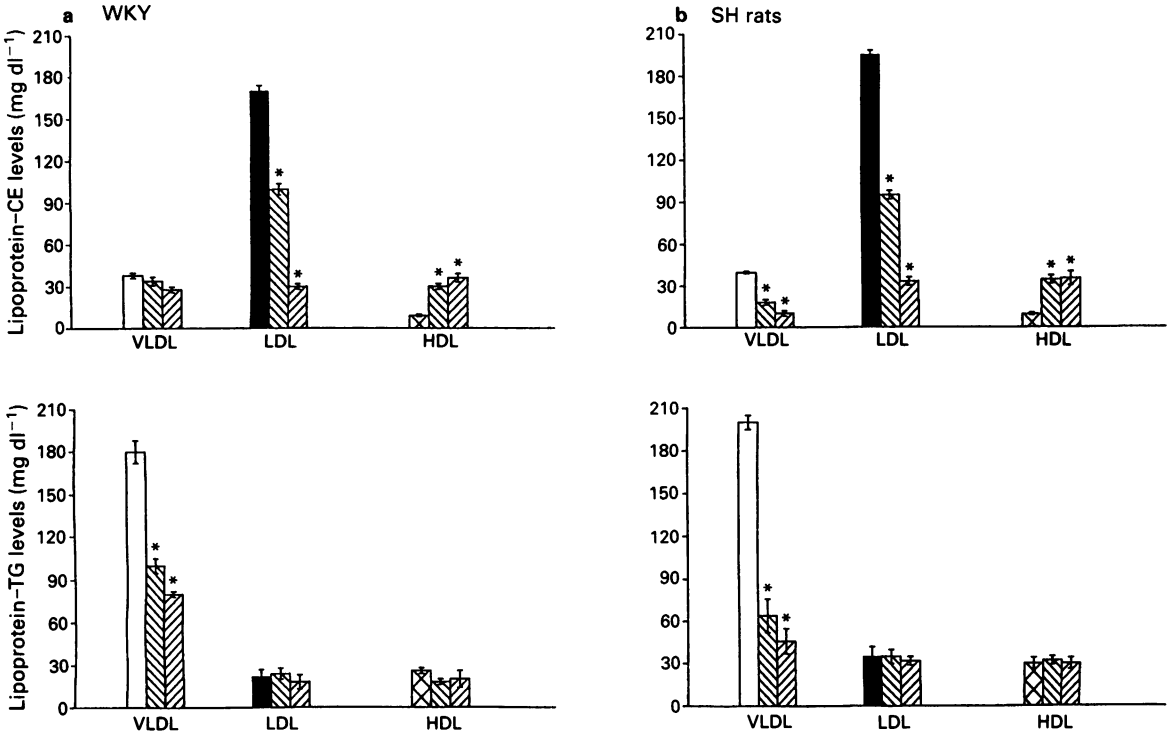

Figure 2 Changes in plasma cholesterol (CE) and triglyceride (TG) concentrations in each lipoprotein fraction (□, VLDL; ■, LDL; ⊠, HDL) produced by dicentrine (▨, 5; ▨ 10 mg kg^{-1}, p.o. twice a day) treatment for 4 weeks in HF-HC diet fed WKY (a) and SH (b) rats. VLDL = very low density lipoprotein; LDL = low density lipoprotein; HDL = high density lipoprotein. Each column represents the mean and vertical bars show s.e.mean ($n = 8-10$). *$P < 0.001$ different from untreated (control) rats.

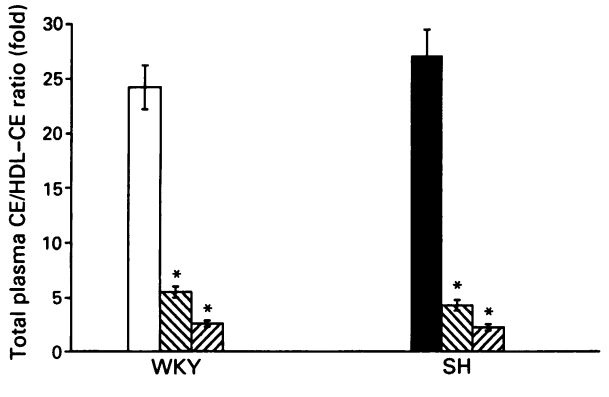

Figure 3 Changes in total plasma cholesterol (CE)/high density lipoprotein (HDL)-CE ratio produced by dicentrine (▨, 5; ▨, 10 mg kg^{-1}, p.o.) treatment for 4 weeks in HF-HC diet fed WKY (□) and SH rats (■). Each column represents the mean and vertical bars show s.e. mean ($n = 8-10$). *$P < 0.001$ different from untreated (control) rats.

Discussion

The results of this study indicate that when fed a HF-HC diet, WKY and SH rats have elevated total plasma CE, TG, decreased HDL-CE levels and dramatically increased CE/HDL-CE ratio as compared with normal chow-fed rats. These data are consistent with those of Uchida *et al.* (1978), who reported that rats hyperrespond to HF-HC feeding. There is evidence from epidaemiological studies that increases in plasma CE, TG and decreases in HDL-CE levels are risk factors for coronary artery disease (Miller & Miller, 1975). The important finding of this study is that dicentrine administration results in reduction of plasma CE, TG, LDL-CE, VLDL-TG and apolipoprotein-B levels while increasing HDL-CE. A strong positive relationship exists between the severity of atherosclerosis and plasma levels of total CE, LDL-CE and its principal apolipoprotein, apolipoprotein-B (Castelli & Anderson, 1986). Plasma TG and VLDL-TG levels have been positively associated with the development of coronary heart disease (CHD) (Krzesinski *et al.*, 1988). On the other hand, a strong inverse relationship has been demonstrated between severity of atherosclerosis and plasma levels of HDL-CE (Wallace *et al.*, 1986). Although several studies show that lowering LDL-CE concentrations reduces the incidence of atherosclerotic disease, it has not been demonstrated that raising HDL-CE concentrations alone will reduce the risk of future disease (Chobanian, 1983; Dall'Aglio *et al.*, 1983). The present study demonstrates that dicentrine not only results in reduction of LDL-CE, but also produces an increase in HDL-CE concentrations, so that higher levels are achieved in dicentrine-treated groups. However, the mechanisms of action of dicentrine-increased HDL-CE levels need further investigation. Thus, in contrast to diuretics and β-blockers which may increase plasma CE, LDL-CE, TG and reduce HDL-CE levels, dicentrine can be used to lower blood pressure in hypertension without the disadvantage of offsetting alterations in the lipoprotein profile. Selective α_1- and β-blockers affect plasma lipid and lipoprotein levels differently (Weinberger, 1986). In general, selective α_1-blockers lead to a more favourable lipid profile than β-blockers. How adrenergic blockade affects these changes is largely unknown. Whether the decrease of plasma TG and CE by dicentrine is due to direct increase of lipoprotein lipase and decrease of HMG-Co A reductase activity needs further investigation.

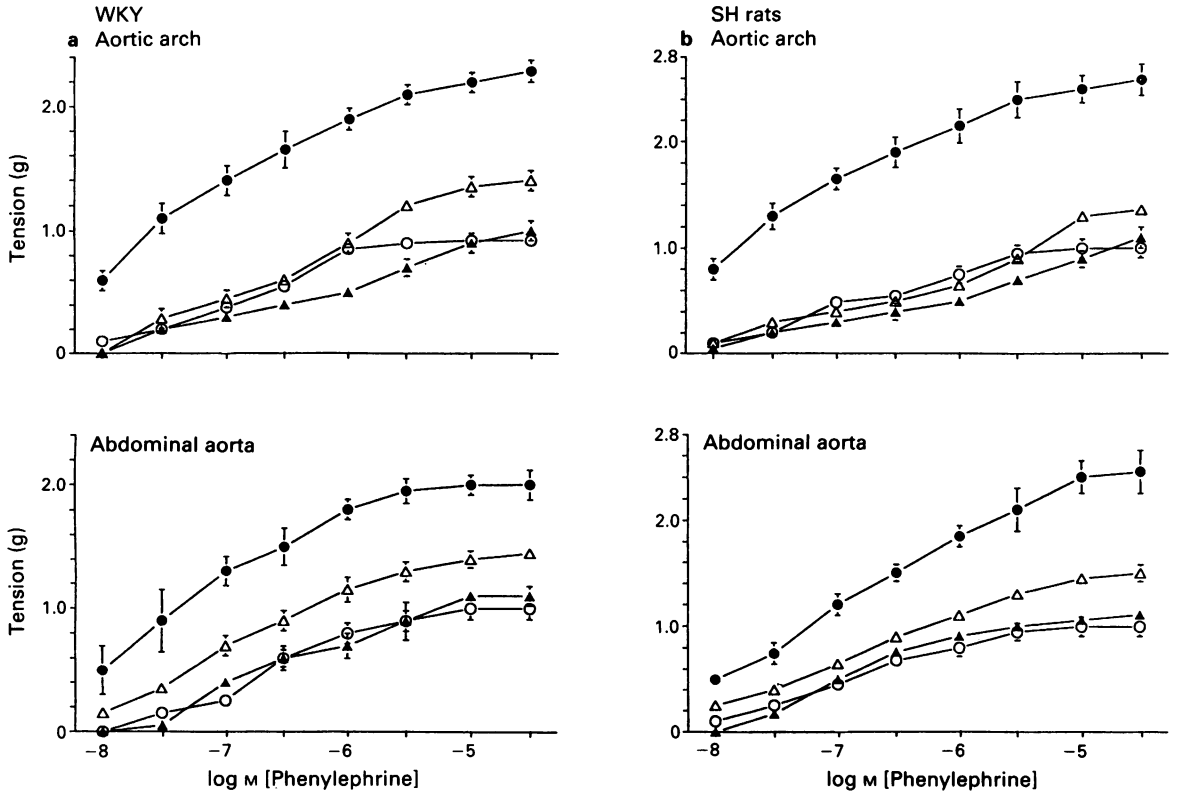

Figure 4 Cumulative concentration-response curves to phenylephrine in aortic arch and abdominal aorta obtained from normal chow (○), HF-HC chow fed rats (WKY, a; SH rats, b) (●) and dicentrine (△, 5; ▲, 10 mg kg^{-1}, p.o.) treatment for 4 weeks in hyperlipidaemic WKY and SH rats. Each point represents the mean and vertical bars show s.e. mean ($n = 6-8$).

Table 3 Effects of dicentrine on the vascular reactivity in aortic arch of WKY and SH rats

		Maximum response			EC_{50} (× 10^{-7} M)		
		PE (g)	*ACh* (% relaxation)	*NP* (% relaxation)	*PE*	*ACh*	*NP*
WKY	Normal chow	0.92 ± 0.09	74.01 ± 4.21	94.01 ± 4.00	2.00 ± 0.12	2.79 ± 0.05	1.59 ± 0.08
	HF-HC chow	2.29 ± 0.15	15.00 ± 3.61	95.01 ± 2.22	0.36 ± 0.08	3.00 ± 0.15	1.55 ± 0.06
	HF-HC chow + Dicentrine 5 mg kg^{-1}	1.4 ± 0.12*	12.00 ± 2.31	93.12 ± 3.00	8.87 ± 0.06*	3.85 ± 0.06	1.45 ± 0.08
	10 mg kg^{-1}	1.0 ± 0.12*	11.00 ± 0.09	96.11 ± 3.61	12.50 ± 0.07*	4.94 ± 0.05*	1.40 ± 0.06
SH	Normal chow	1.00 ± 0.08	70.21 ± 3.65	96.51 ± 3.59	1.79 ± 0.23	3.10 ± 0.06	1.58 ± 0.07
	HF-HC chow	2.59 ± 0.14	11.00 ± 3.62	89.00 ± 3.00	0.32 ± 0.03	3.10 ± 0.04	1.89 ± 0.09
	HF-HC chow + Dicentrine 5 mg kg^{-1}	1.36 ± 0.08*	9.51 ± 0.08	93.61 ± 2.33	11.70 ± 0.12*	3.86 ± 0.05	1.98 ± 0.06
	10 mg kg^{-1}	1.09 ± 0.14*	11.01 ± 2.00	95.00 ± 2.41	16.75 ± 0.14*	4.86 ± 0.04*	1.99 ± 0.07

Values are means ± s.e. mean for n observations ($n = 9$). PE, phenylephrine; ACh, acetylcholine; NP, nitroprusside; HF-HC, high fat-high cholesterol.
*$P < 0.001$ denotes significantly different from data obtained from high fat-high cholesterol chow dicentrine-untreated animals.

Results from several studies have demonstrated that there is a greater sympathetic activity and noradrenaline concentration in SH rats (Yu *et al.*, 1992). This may explain why oral administration of dicentrine evoked greater decreases in MAP and contraction to phenylephrine in SH rats and supports the concept that dicentrine acts via inhibition of α-adrenoceptor activity. Hyperlipidaemia is known to enhance the sensitivity of the circulatory system to adrenergic stimulus (Rosendorff *et al.*, 1981; Heistad *et al.*, 1984); Broderick & Tulenko (1984) for example, reported that dose-response changes in coronary vascular resistance with noradrenaline was shifted to the left in hyperlipidaemic rats. They suggested that this could be due to an increase in either the number or affinity of the α-adrenoceptors. The results of the present study show an enhanced vasoconstrictor responsiveness to phenylephrine in rats with high levels of plasma lipid. Although the mechanism of these responses remains to be determined, the data suggest that adrenergic vascular control is altered in the presence of high levels of plasma lipid. The vascular sensitivity to phenylephrine was increased in hyperlipidaemic rats, thus α_1-adrenoceptor blockade with dicentrine produced significantly attenuated maximal responses and augmented EC_{50} values for phenylephrine.

In hyperlipidaemic rat aortae, endothelium-dependent re-

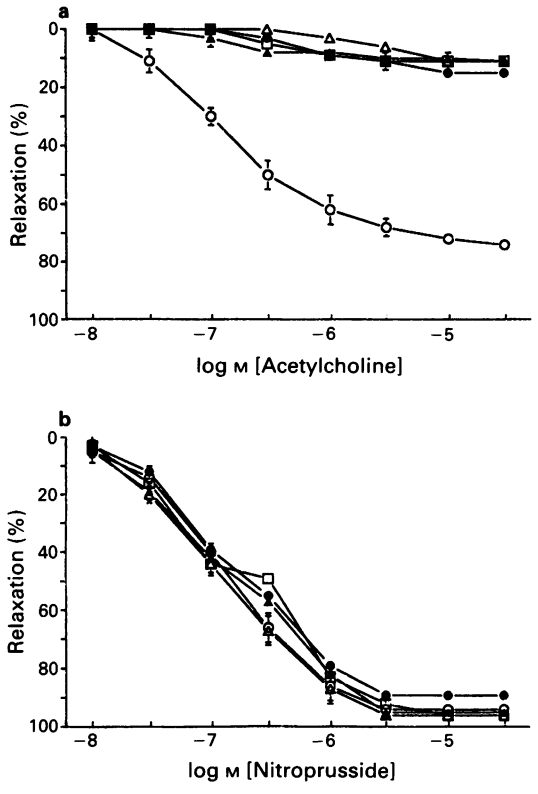

Figure 5 Endothelium-dependent relaxation to acetylcholine (a) and endothelium-independent relaxation to nitroprusside (b) in aortic arch obtained from normal chow (○), HF-HC chow fed rats (WKY ●; SH rats △) and dicentrine (▲, 5; □, 10 mg kg^{-1}, p.o.) treatment for 4 weeks in hyperlipidaemic WKY and SH rats. Each point represents the mean and vertical bars show s.e. mean ($n = 6-8$).

laxation to acetylcholine was decreased and was progressively attenuated during atherosclerotic progression, while relaxation to nitroprusside was well preserved. There are a number of reports which demonstrate that endothelium-dependent relaxation is impaired in atherosclerotic arteries obtained from animals and man (Hirata *et al.*, 1992). There are several possible mechanisms for the impairment of endothelium-dependent relaxation in atherosclerotic arteries. First, the production and/or release of endothelium-derived relaxing factor (EDRF) may be decreased. Second, the thickened intima may reduce the diffusion of EDRF, the half-life of which is extremely short. Third, the characteristics of smooth muscle cells and their sensitivity to EDRF may be changed. The last possibility is unlikely because the relaxation to nitroprusside, which induces relaxation through activation of guanylate cyclase in smooth muscle cells as does EDRF, was well maintained in atherosclerotic arteries. Recently, Kolodgie *et al.* (1990) have demonstrated that endothelium-mediated relaxation is reduced in hyperlipidaemic rabbits because of a loss of endothelial cells. At present, precise mechanisms for the attenuation of EDRF-mediated relaxation in atherosclerotic arteries are still debated.

In conclusion, dicentrine decreases MAP, plasma CE, LDL-CE, apolipoprotein-B, plasma TG, VLDL-TG, vascular hyperreactivity to phenylephrine and increases HDL-CE levels. Dicentrine may thus hold potential for the reduction of two of the major risk factors, hypertension and hyperlipidaemia, for cardiovascular disease.

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