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Vascular Responses to Sodium Arachidonate in Experimental Hypertension (42039)

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Abstract. This study characterizes vascular responsiveness to sodium arachidonate (C 20:4) in four models of hypertension [deoxycorticosterone acetate (DOCA) hypertensive rats, two kidney-one clip (2K-1C) renal hypertensive rats, spontaneously hypertensive rats (SHR), and psychosocial hypertensive mice]. Isolated arterial strips (aorta, mesenteric artery, tail artery) were equilibrated under optimal resting tension in physiological salt solution for measurement of isometric force generation. Dose–response curves to arachidonate (10^{-10} to 10^{-4} g/ml) in arteries from DOCA and 2K-1C hypertensive rats were shifted to the left compared to those in arteries from control rats. In arteries from SHR and psychosocial hypertensive mice, the dose–response relationships were unchanged compared to normotensive values. Arteries from DOCA hypertensive and 2K-1C hypertensive rats developed greater maximal contractile responses to arachidonate than controls; maximal responses in arteries from SHR and psychosocial hypertensive mice were unchanged compared to normotensive values. Contractions to arachidonate were inhibited by indomethacin (0.5 and 5 μg/ml) and by aspirin (5 and 50 μg/ml). The fatty acid, oleate (C 18:1), had no effect on the contractile state of the arteries, whereas prostaglandin $F_{2\alpha}$ caused contraction. These results indicate altered responsiveness to exogenous arachidonate in arteries from DOCA and 2K-1C hypertensive rats, but not in arteries from SHR and psychosocial hypertensive mice.

Prostaglandins modulate the responsiveness of vascular smooth muscle (1) and it has been proposed that alterations in the synthesis of prostaglandins contribute to increased vascular resistance in hypertension (2, 3). The synthesis of prostaglandin E-like substances is depressed in kidneys of rats made hypertensive by renal artery stenosis (4) or salt loading (5) whereas the generation of prostacyclin and prostaglandin E-like substances from exogenous arachidonate is augmented in isolated blood vessels from spontaneously hypertensive rats (6–8). The overall objective of the current study was to evaluate the vasoactive properties of prostanoids synthesized from exogenous arachidonate in hypertension. The experiments were performed on isolated arterial strip preparations (aorta, mesenteric artery, tail artery) from animals with four different types of hypertension [deoxycorticosterone acetate (DOCA) hypertensive rats, two kidney-one clip (2K-1C) renal hypertensive rats, spontaneously hypertensive rats (SHR), and psychosocial hypertensive mice].

Methods. *Animal models of hypertension.* Adult, male spontaneously hypertensive rats (SHR), Wistar–Kyoto normotensive rats (WKY), Sprague–Dawley rats, and CBA mice were used. The SHR and WKY (250–300 g) were obtained from Charles River Breeding Laboratories, Wilmington, Massachusetts. Sprague–Dawley rats (250–300 g) were made hypertensive by two different techniques: (a) six rats were anesthetized with ether, uninephrectomized, and received subcutaneous implantations of deoxycorticosterone acetate (DOCA, 200 mg/kg, Sigma Chemical Co.) impregnated in silastic strips (Dow Corning Co.); these rats received 1% NaCl, 0.2% KCl in their drinking water; (b) six rats were anesthetized with ether and the left kidney was exposed through a flank incision; a silver block (0.22-mm slit) was placed on the left renal artery and tied in place. Control, normotensive Sprague–Dawley rats did not undergo sham treatment and received normal tap water for drinking. All rats were maintained on standard rat chow (Purina). Systolic blood pressures were measured in the unanesthetized state by the tail cuff technique (pneumatic detector). Experiments were performed at 4–6 weeks after surgery in Sprague–Dawley rats.

Male CBA Agouti mice were made hypertensive by psychosocial stimulation as de-

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scribed by Henry *et al.* (9). Briefly, the young were weaned at 18–21 days and then placed individually into 0.5-liter glass jars. At 4 months, these "isolates" were placed into special population cages along with an equal number of nonisolated females and males of the same age; these cages consist of six standard boxes formed into a circle by narrow connecting tubes with a central feeding and watering place connected to each box by radial spokes. The males, under these conditions, are highly aggressive, fail to establish a social hierarchy, and develop hypertension within the first week. The duration of social interaction in the population cage was 2 months. Male mice raised in a traditional laboratory manner served as controls. Systolic blood pressures were measured in the unanesthetized state by a tail cuff technique as described previously (10). All mice were fed a standard commercial diet (Purina).

Tissue preparation. Rats were anesthetized with sodium pentobarbital (50 mg/kg, ip) and aortae, mesenteric arteries, and tail arteries were excised. Mice were anesthetized with ether and aortae were excised. The arteries were stored in physiological salt solution (PSS) and cut helically into strips (0.8 to 1.0 × 10 mm) under a dissecting microscope. The helical strips were mounted vertically on a glass holder in a tissue bath containing PSS. The upper ends of the strips were connected to force transducers (Grass FT.03) and the resting tension of each strip was adjusted so that it developed maximum active force in response to a standard dose of norepinephrine. Before the start of experimentation, the strips were allowed to equilibrate in PSS for 90–120 min. The bathing medium was maintained at 37°C and aerated with a mixture of 95% O_2 and 5% CO_2. The pH of the PSS was 7.2 and the composition (in mmole/liter) was as follows: NaCl, 130; KCl, 4.7; KH_2PO_4, 1.18; $MgSO_4$-$7H_2O$, 1.17; $CaCl_2$-$2H_2O$, 1.6; $NaHCO_3$, 14.9; dextrose, 5.5; and $CaNa_2$ EDTA, 0.03. Higher concentrations of potassium (25 and 100 m*M*) in the bathing medium were achieved by equimolar substitution of NaCl with KCl.

Statistical analysis. Data are reported as the means ± standard error of the mean (SEM). For calculation of ED_{50} values (concentration which caused a half maximal response), contractile responses were expressed as a percentage of the maximal response before a logit-log transformation was performed. Transformed data were curve fitted using an unweighted least-squares linear regression. An unpaired analysis (Student's *t* test) was used to compare blood pressures (Table I), absolute maximal force responses (Table II), and ED_{50} values (Table III) between animal groups. A paired *t* test was used to compare the effects of drugs on contractile responses to different agonists (e.g., comparison of the effect of indomethacin on contractile responses to norepinephrine in aortic strips). Dose–response curves to sodium arachidonate (as percentage maximal response to $PGF_{2\alpha}$) were analyzed by two-way analysis of variance (Figs. 1–3). The significance level for all analyses was $P < 0.05$.

Drugs. Drugs used were norepinephrine bitartrate (Breon Laboratories, Inc.), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, Tris salt, Sigma Chemical Co.), sodium arachidonate (Sigma Chemical Co.), sodium oleate (Sigma Chemical Co.), prostacyclin (PGI_2, sodium salt, Sigma Chemical Co.), phentolamine mesylate (Ciba Pharmaceutical Co.), aspirin (generic brand supplied by University of Michigan Pharmacy), and indomethacin (Sigma Chemical

TABLE I. ANIMAL CHARACTERISTICS

Animal	Body weight (g)	Systolic blood pressure (mm Hg)
Sprague–Dawley normotensive rats ($N = 6$)	323 ± 12	120 ± 2
DOCA hypertensive rats ($N = 6$)	276 ± 4*	178 ± 3*
2K-1C hypertensive rats ($N = 6$)	290 ± 5	168 ± 3*
WKY ($N = 6$)	283 ± 7	128 ± 3
SHR ($N = 6$)	278 ± 6	183 ± 2*
Normotensive mice ($N = 6$)	34 ± 3	124 ± 2
Psychosocial hypertensive mice ($N = 6$)	33 ± 2	158 ± 5*

Note. Values are the means ± SEM. Values in parentheses are the number of animals. Asterisks indicate statistically significant differences between hypertensive animals and respective normotensive animals ($P < 0.05$).

TABLE II. MAXIMAL CONTRACTILE RESPONSES TO NOREPINEPHRINE, $PGF_{2\alpha}$, AND SODIUM ARACHIDONATE

Animal	Preparation	Maximal force developed (mg) NE (3×10^{-6} g/ml)	$PGF_{2\alpha}$ (3×10^{-5} g/ml)	SA (10^{-5} g/ml)
Sprague–Dawley normotensive rats ($N = 6$)	Aorta	871 ± 63	877 ± 37	203 ± 53
	Mesenteric artery	568 ± 44	505 ± 36	72 ± 32
	Tail artery	2256 ± 87	893 ± 129	0
DOCA hypertensive rats ($N = 6$)	Aorta	748 ± 65	823 ± 53	790 ± 44*
	Mesenteric artery	469 ± 33	450 ± 54*	312 ± 60*
	Tail artery	1565 ± 117*	833 ± 91	130 ± 45*
2K-1C, renal hypertensive rats ($N = 6$)	Aorta	650 ± 49*	853 ± 80	712 ± 24*
	Mesenteric artery	392 ± 48*	468 ± 45	296 ± 40*
	Tail artery	1768 ± 205*	842 ± 71	69 ± 42*
WKY ($N = 6$)	Aorta	1060 ± 75	1020 ± 130	528 ± 119
	Mesenteric artery	677 ± 42	527 ± 51	87 ± 30
	Tail artery	1718 ± 199	949 ± 106	6 ± 4
SHR ($N = 6$)	Aorta	967 ± 107	1063 ± 150	553 ± 110
	Mesenteric artery	487 ± 37*	433 ± 51	111 ± 20
	Tail artery	1391 ± 126*	826 ± 105	15 ± 8
Psychosocial hypertensive mice ($N = 6$)	Aorta	472 ± 28	463 ± 37	100 ± 21
Normotensive mice ($N = 6$)	Aorta	493 ± 12	473 ± 58	115 ± 34

Note. Values are the means ± SEM. Asterisks indicate a statistically significant difference between respective arteries from hypertensive and normotensive animals (unpaired t test; $P < 0.05$). NE = norepinephrine; SA = sodium arachidonate.

TABLE III. ED_{50} VALUES FOR SODIUM ARACHIDONATE

Animal	ED_{50} value (μg/ml) Aorta	Mesenteric artery	Tail artery
Sprague–Dawley Normotensive rats ($N = 6$)	21.09 ± 13.01	6.13 ± 2.44	—
DOCA hypertensive rats ($N = 6$)	0.04 ± 0.01*	0.04 ± 0.02*	0.39 ± 0.15
2K-1C hypertensive rats ($N = 6$)	0.44 ± 0.18*	0.46 ± 0.08*	1.05 ± 0.44
WKY ($N = 6$)	1.38 ± 0.45	4.20 ± 1.91	—
SHR ($N = 6$)	1.74 ± 1.00	1.60 ± 0.49	—
Normotensive mice ($N = 6$)	0.47 ± 0.16	—	—
Psychosocial hypertensive mice ($N = 6$)	0.54 ± 0.19	—	—

Note. Values are the means ± SEM. Individual ED_{50} values were computed following logit transformation. Asterisks indicate statistically significant differences between hypertensive and normotensive values ($P < 0.05$).

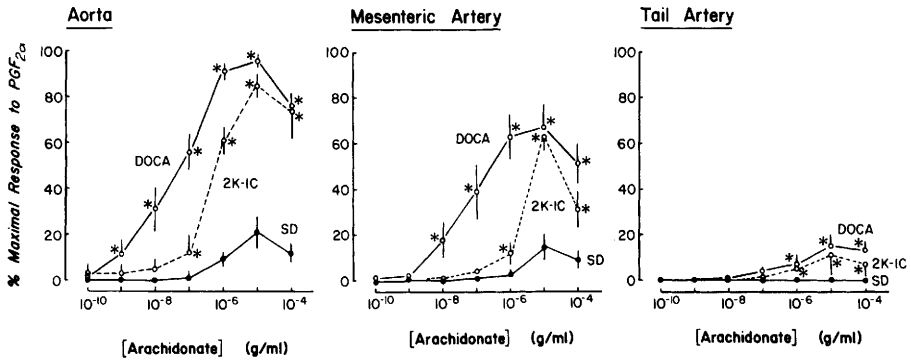

FIG. 1. Vascular responses to sodium arachidonate in DOCA hypertensive and 2K-1C, renal hypertensive rats. Mean contractile responses of hypertensive preparations that are significantly greater than in normotensive preparations are denoted by asterisks ($P < 0.05$). Values are the means ± SEM for six normotensive rats, six DOCA hypertensive rats, and six 2K-1C, renal hypertensive rats.

Co.). Prostacyclin was dissolved in 0.5 m*M* glycine buffer. Norepinephrine, $PGF_{2\alpha}$, aspirin, and phentolamine were dissolved in water; sodium arachidonate and sodium oleate were dissolved in 100 m*M* Na_2CO_3 buffer in a concentration of 10 mg/ml. Ethanol, in the concentration used in these experiments (0.1%), had no effect on contractile responses of the helical strips to norepinephrine, potassium chloride, sodium arachidonate, or $PGF_{2\alpha}$.

Results. *Animals.* At the time of experimentation, the systolic blood pressures of SHR, DOCA-treated rats, rats with renal artery clips, and male mice raised in population cages were significantly higher than those of respective control animals (Table I).

Passive force and contractile responses to norepinephrine. Before the start of experimentation, the arterial strips were stretched to successively greater levels of passive force. At each 100-mg increment in passive force applied to the strips, contractile responses to 10^{-7} or 10^{-8} g/ml norepinephrine were determined. The optimum passive force for generation of active contractile responses was defined as that passive force which gave no further increase in active force generation for two successive 100-mg increments. The optimum passive force for maximum response to norepinephrine was similar for arterial strips from hypertensive animals and those from normotensive animals: (a) Sprague–Dawley normotensive rats ($N = 6$), aorta

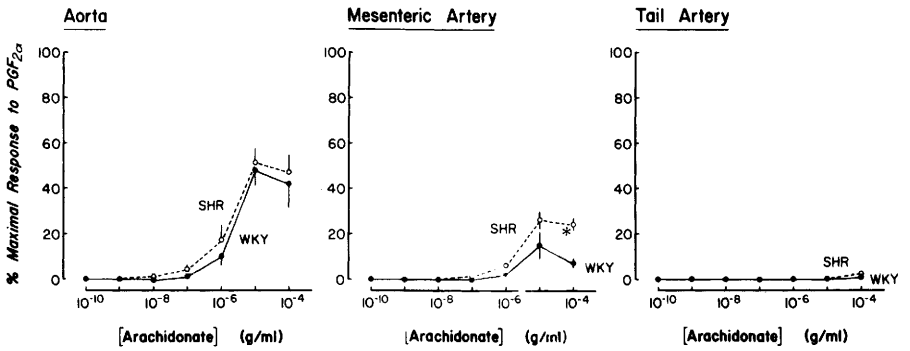

FIG. 2. Vascular responses to sodium arachidonate in SHR. Mean contractile responses of SHR preparations that are significantly greater than in normotensive preparations are denoted by asterisks ($P < 0.05$). Values are the means ± SEM for six SHR and six WKY.

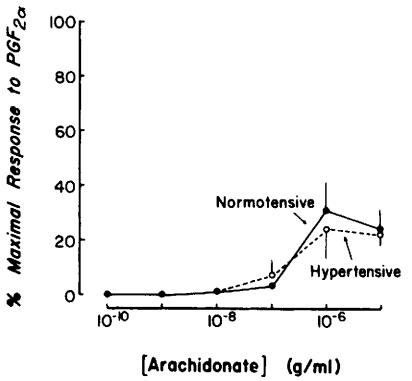

FIG. 3. Vascular responses to sodium arachidonate in psychosocial hypertensive mice. At all doses of arachidonate, there was no significant difference in the contractile responses of aortae from psychosocial hypertensive mice and those from normotensive mice. Values are the means ± SEM for six hypertensive and six normotensive mice.

= 1508 ± 36 mg, mesenteric artery = 508 ± 26 mg, tail artery = 600 ± 14 mg; (b) DOCA hypertensive rats (N = 6), aorta = 1516 ± 37 mg, mesenteric artery = 492 ± 26 mg, tail artery = 583 ± 18 mg; (c) 2K-1C, renal hypertensive rats (N = 6), aorta = 1551 ± 30 mg, mesenteric artery = 495 ± 22 mg, tail artery = 588 ± 13 mg; (d) WKY (N = 6), aorta = 1518 ± 18 mg, mesenteric artery = 510 ± 13 mg, tail artery = 597 ± 13 mg; (e) SHR (N = 6), aorta = 1513 ± 40 mg, mesenteric artery = 525 ± 20 mg, tail artery = 608 ± 15 mg; (f) psychosocial hypertensive mice (N = 6), aorta = 550 ± 56 mg; and (g) normotensive mice (N = 6), aorta = 558 ± 26 mg.

Contractile responses to sodium arachidonate. In all figures, contractile responses to sodium arachidonate are expressed as a percentage of the maximal response to $PGF_{2\alpha}$ to allow comparisons between different arterial preparations. Absolute maximal forces developed to $PGF_{2\alpha}$ (3×10^{-5} g/ml) and to norepinephrine (3×10^{-6} g/ml) in arterial preparations from hypertensive animals were either less than or similar to those in arterial preparations from respective control animals (Table II). Cumulative addition of sodium arachidonate (10^{-10} to 10^{-4} g/ml) to the muscle bath produced contractile responses in aortic and mesenteric artery strips from hypertensive and normotensive animals (Figs. 1–3). Tail artery strips from DOCA hypertensive and 2K-1C, renal hypertensive rats contracted in response to sodium arachidonate, whereas tail artery strips from normotensive Sprague–Dawley rats did not (Fig. 1, Table II). Tail arteries from SHR and WKY contracted only at the highest dose of sodium arachidonate (Fig. 2, Table II). Maximal contractile responses to sodium arachidonate were greater in arterial strips from DOCA hypertensive and 2K-1C, renal hypertensive rats than in those isolated from normotensive Sprague–Dawley rats (Table II). Maximal contractile responses to sodium arachidonate in arterial strips from SHR and psychosocial hypertensive mice were not different from those in arterial strips from their respective control groups (Table II). Contractile responses to sodium arachidonate were not inhibited by the α-adrenergic antagonist, phentolamine (for example, aortic strips from normotensive rats: contractile response to 10^{-5} g/ml sodium arachidonate before treatment with phentolamine = 23 ± 8% maximal response to $PGF_{2\alpha}$; contractile response after treatment with 10^{-6} M phentolamine = 22 ± 7%; N = 6).

To allow interpretation of the results in terms of sensitivity to agonist concentration, the contractile responses for each arterial strip were normalized to its maximal response and the concentration of sodium arachidonate producing a half-maximal response (ED_{50}) was determined (Table III). Arterial strips from DOCA hypertensive and 2K-1C, renal hypertensive rats were more sensitive to the prostaglandin precursor than those from normotensive Sprague–Dawley rats. ED_{50} values for sodium arachidonate in arterial strips from SHR and psychosocial hypertensive mice were not different from those measured in arterial strips from respective normotensive animals.

Figure 4 shows the format of the technique used to determine the effect of cyclooxygenase inhibitors (indomethacin and aspirin) on the contractile response to sodium arachidonate. An aortic strip from a DOCA hypertensive rat (bottom tracing) and one from a normotensive rat (top tracing) were made to contract in response to a dose of sodium arachidonate (10^{-5} g/ml) which produced a maximal con-

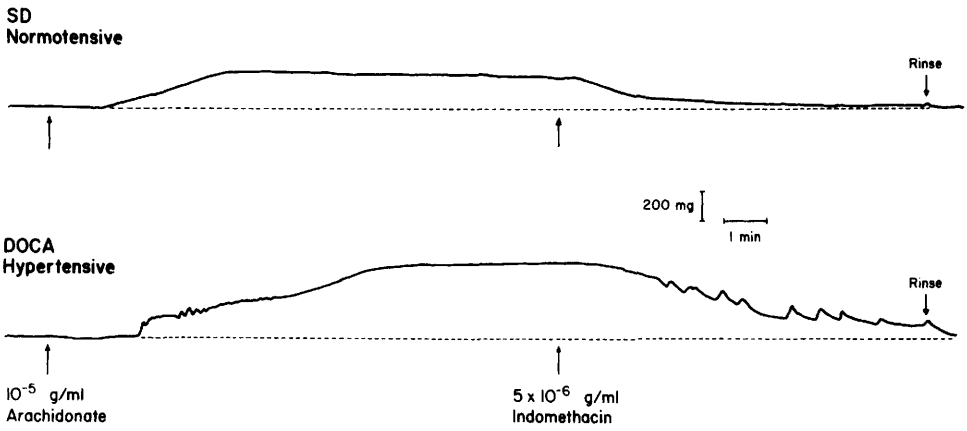

FIG. 4. Inhibition by indomethacin. Indomethacin (5 μg/ml) inhibited contractile responses to sodium arachidonate in aortic strips from DOCA hypertensive and normotensive rats (see Results for details).

traction. After the contractile response had plateaued, indomethacin (5 μg/ml) was added to the muscle bath and relaxation occurred in both aortic strips. Contractile responses to sodium arachidonate were inhibited by indomethacin in all arterial strip preparations. Aspirin (50 μg/ml) also inhibited contractile responses to sodium arachidonate (data not shown). Lower doses of indomethacin (0.5 μg/ml) and aspirin (5 μg/ml) also caused relaxation of contractile responses to sodium arachidonate (10^{-5} g/ml) in aortic and mesenteric artery strips. The relaxation to these lower doses of the drugs was slower in onset compared to the high doses; maximal relaxation was achieved at approximately 15–20 min after drug addition. Maximal contractile responses to norepinephrine (3×10^{-6} g/ml), $PGF_{2\alpha}$ (3×10^{-5} g/ml), and potassium chloride (100 m*M*) in all three vascular preparations were not altered by the cyclooxygenase inhibitors. Additionally, submaximal contractile responses to elevated potassium (25 m*M*) in aortic and mesenteric artery strips from normotensive rats were not altered by indomethacin or aspirin. In contrast, submaximal contractile responses to norepinephrine (10^{-8} g/ml) and $PGF_{2\alpha}$ (10^{-8} g/ml) in mesenteric artery strips were reduced by the cyclooxygenase inhibitors. This inhibitory effect was related to the dose of the cyclooxygenase inhibitor (15-min treatment before addition of norepinephrine or $PGF_{2\alpha}$; $N = 4$ for all values): (a) control response to 10^{-8} g/ml norepinephrine in the presence of 0.1% ethanol (vehicle) = 296 ± 37 mg; (b) response to 10^{-8} g/ml norepinephrine in the presence of 0.5 μg/ml indomethacin = 233 ± 27 mg (paired *t* test; $P < 0.05$); (c) response to 10^{-8} g/ml norepinephrine in the presence of 5 μg/ml indomethacin = 118 ± 21 mg (paired *t* test; $P < 0.05$; (d) contractile response to 10^{-8} g/ml $PGF_{2\alpha}$ in the presence of 0.1% ethanol = 248 ± 37 mg; (e) response to 10^{-8} g/ml $PGF_{2\alpha}$ in the presence of 0.5 μg/ml indomethacin = 170 ± 31 (paired *t* test; $P < 0.05$); and (f) response to 10^{-8} g/ml $PGF_{2\alpha}$ in the presence of 5 μg/ml indomethacin = 78 ± 10 mg (paired *t* test; $P < 0.05$). Since the cyclooxygenase inhibitors did not alter submaximal or maximal contractile responses to potassium chloride, it is concluded that the inhibitory effect of indomethacin and aspirin on contractile responses to sodium arachidonate is not due to a nonspecific action of the drugs on the smooth muscle. The observation that submaximal contractile responses to norepinephrine and $PGF_{2\alpha}$ are attenuated by the inhibitors suggests that these smooth muscle agonists mobilize vasoactive prostanoids.

Treatment with sodium oleate. To test the possibility that contractile responses to sodium arachidonate were due to a nonspecific effect of the fatty acid, arterial strips from all groups of rats were treated with sodium oleate (10^{-4} g/ml). This fatty acid had no effect on the contractile state of the arterial segments ($N = 3$ for each group, data not shown).

Relaxant responses to sodium arachidonate and prostacyclin. In addition to causing contraction from basal tension, sodium arachidonate can cause dose-dependent relaxation of contractile responses induced by norepinephrine. In these experiments, mesenteric artery strips from normotensive rats were made to contract in response to 10^{-8} g/ml norepinephrine (force developed = 312 ± 42 mg; N = 4). Once this contraction had reached a plateau, sodium arachidonate (10^{-10} to 10^{-4} g/ml) was added to the muscle bath in a cumulative manner. At the lowest doses of the fatty acid (10^{-10} and 10^{-9} g/ml) there was no change in the contractile response to norepinephrine; intermediate doses of sodium arachidonate (10^{-8} to 10^{-6} g/ml) caused relaxation (percentage change from norepinephrine-induced contraction: 10^{-8} g/ml arachidonate = −8 ± 3%; 10^{-7} g/ml arachidonate = −24 ± 5%; 10^{-6} g/ml arachidonate = −32 ± 8%); and the highest doses of sodium arachidonate caused contractions [percentage change from norepinephrine-induced contraction: 10^{-5} g/ml arachidonate = −18 ± 8% (contraction compared to previous dose of the fatty acid); 10^{-4} g/ml arachidonate = 22 ± 8%]. Both the relaxant and contractile responses to sodium arachidonate were inhibited by indomethacin (0.5 μg/ml; added 15 min before contraction induced by norepinephrine). These experiments demonstrate that the arterial segments used in these experiments are capable of generating both constrictor and dilator prostaglandins.

Prostacyclin (10^{-7} g/ml) caused relaxation of norepinephrine-induced contractions (10^{-9} g/ml) in mesenteric artery strips from normotensive rats. The magnitude of contraction induced by norepinephrine was 294 ± 37 mg (N = 4), and the magnitude of relaxation in response to prostacyclin was a −38 ± 4% change from the contractile response. The relaxation induced by prostacyclin was transient lasting approximately 2 to 3 min in all arterial preparations.

Discussion. This study demonstrates that in two models of experimental hypertension (DOCA hypertensive rats and 2K-1C, renal hypertensive rats), exogenous arachidonate is more effective in producing contraction of isolated vascular strips than in those from normotensive controls. Contractile responses to sodium arachidonate in strip preparations from SHR and psychosocial hypertensive mice were not different than those in strips from respective control animals. In addition to causing contraction from basal tension, sodium arachidonate caused dose-dependent relaxation of norepinephrine-induced contractile responses in mesenteric arteries from normotensive rats. Indomethacin and aspirin blocked contractile and relaxant responses to sodium arachidonate, and the fatty acid, oleate, had no contractile effect suggesting that arachidonate is converted to vasoactive prostaglandins.

It is doubtful that the difference in contractile responsiveness to sodium arachidonate is caused by a difference in the amount of preload (i.e., existence of hypertension) or passive force placed on the arterial strips from the hypertensive animals. The optimum passive force for maximum response to norepinephrine was similar for arterial strips from hypertensive and control animals. Furthermore, maximal responses to norepinephrine and $PGF_{2\alpha}$ in arterial strips from hypertensive animals were either less than or similar to those in arteries from normotensive controls. A difference in the length–tension relationship would be predicted to result in a generalized change in contractility. Thus, the experimental observations suggest that a specific change in force generating ability in response to exogenous arachidonate occurs in blood vessels of DOCA hypertensive and 2K-1C, renal hypertensive rats.

An alteration in the enzymatic pathway for conversion of arachidonate to the vasoactive prostaglandins could account for the augmented responsiveness of isolated vascular strips from DOCA hypertensive and 2K-1C, renal hypertensive rats to the precursor. This change in enzymatic conversion could occur at both the level of the smooth muscle cell and/or the endothelium. The current study does not allow a separation of these components since the endothelium was not removed from the vascular preparations (as evidenced by relaxation responses to acetylcholine; data not shown). Alternatively, altered vascular responsiveness to sodium arachidonate in hypertension may reflect changes in any of

the following cellular processes: (a) degradation of vasoactive prostaglandins; (b) synthetic profile of constrictor and dilator prostaglandins; (c) incorporation of arachidonate into the cell membranes; and/or (d) sensitivity to the generated products.

Experimental studies implicating alterations in prostaglandin synthesis in hypertension are most variable. Laborit and Valette (11) observed that administration of arachidonic acid increased blood pressure by 25–37% in DOCA hypertensive rats. Cyclooxygenase blockade lowered blood pressure in these rats. In contrast, Pugsley *et al.* (4) reported that cyclooxygenase blockade aggravates hypertension in 1K-1C, renal hypertensive rats. Lessening of the severity of hypertension induced by bilateral renal artery stenosis has been observed in rats when a cyclooxygenase inhibitor was administered before the development of increased blood pressure (12). Yun *et al.* (13) reported that cyclooxygenase blockade lowers blood pressure in dogs with chronic renovascular hypertension. Romero and Strong (14) observed that the blood pressure response to indomethacin depended upon the level of renal function in 2K-1C, renal hypertensive rabbits. In hypertensive rabbits with severe impairment of renal circulation, the administration of indomethacin caused renal insufficiency and elevated blood pressure associated with either volume expansion or increased plasma renin activity. Scholkens and Steinbach (15) have observed that indomethacin aggravates 2K-2C, renal hypertension in the rat and Levy (16) has reported that cyclooxygenase inhibitors cause a significant elevation in blood pressure of SHR but not WKY. Dusting *et al.* (17) concluded that rats with 1K-1C, renal hypertension have an enhanced ability to convert exogenous arachidonic acid into vasodilator prostaglandins. They observed that vasodepressor effects of arachidonic acid were greater and more prolonged in hypertensive rats than in normotensive controls. Morera *et al.* (18) have reported that the initial phase of hypertension in rats with bilateral renal artery stenosis is characterized by increased synthesis of prostacyclin in the aorta. During the established phase of the hypertension, prostacyclin synthesis in aortae from hypertensive rats did not differ from controls. The results of the current study suggest that isolated blood vessels from DOCA hypertensive and 2K-1C, renal hypertensive rats have an increased capacity to convert exogenous arachidonate to vasoconstrictor prostaglandins. Alternatively, the blood vessels from these animals synthesize less vasodilator prostaglandins than in those from control animals which unmasks an augmented contractile response to the precursor. The vascular preparations used in the current experiments relax in response to prostacyclin and sodium arachidonate but a comparative study using hypertensive and normotensive animals has not been performed.

An increased responsiveness of the smooth muscle cells to the contractile effects of the synthesized prostaglandins may also contribute to the augmented response to exogenous arachidonate in isolated blood vessels from DOCA hypertensive and 2K-1C, renal hypertensive rats. In general, constrictor responses to various prostaglandins are augmented in the vasculature of hypertensive animals (19, 20). However, the results of different studies are highly variable. Greenberg (21) has observed an increased sensitivity (lower ED_{50} value) to PGH_2 and PGB_2 in various arteries and veins from 2K-1C, renal hypertensive dogs. Levy (22) reported that the contractile effects of PGE_2 and $PGF_{2\alpha}$ are reduced in aortic strips from SHR. The results of the current study suggest that the maximal force generating ability in response to $PGF_{2\alpha}$ in various arteries from hypertensive animals are either less or similar to that in those from normotensive controls. Since the sensitivity (lower ED_{50} value) of the vasculature to prostaglandins is increased in hypertension, a portion of the augmented response to exogenous arachidonate is likely to reflect this change in smooth muscle function.

An interesting observation of this study is that the magnitude of the change in responsiveness to arachidonate is inversely correlated with the catecholamine content of the arterial preparation [i.e., tail arteries have a high catecholamine content (23) but contract the least in response to arachidonate; aortic strips contain the least norepinephrine (24) but

contract the most to arachidonate; mesenteric arteries are intermediate in catecholamine content (24) and in responsiveness to arachidonate]. This relationship between adrenergic innervation (catecholamine content) and responsiveness to the prostaglandin precursor may be important since the catecholamine content of arteries from DOCA hypertensive (24) and 2K-1C, renal hypertensive rats (23) is lower than in those from normotensive rats. In SHR, catecholamine content of the vessel wall is unchanged compared to WKY (25), and contractile responses to arachidonate are not altered in this genetic model of hypertension. Thus, the responsiveness to arachidonate may be related to a change in adrenergic nerve function.

Whatever the molecular mechanisms involved, these findings are significant in that they demonstrate a change in vascular responsiveness to arachidonate in two models of experimental hypertension. This altered responsiveness to the prostaglandin precursor may reflect changes in any of the following: (a) synthetic or degradative pathways; (b) sensitivity to the generated products; (c) synthetic profile of constrictor and dilator prostaglandins; (d) incorporation of arachidonate into the cell membrane; and/or (e) synthetic differences in endothelial and smooth muscle components of the vascular wall. It should be noted that since the current experiments were performed on large blood vessels, it is difficult to extrapolate the results to blood pressure regulation in the intact animal. The profile of arachidonate-derived products may differ in the resistance vessels and/or the effects of these products may be different at this level of the vasculature.

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