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Changes in Renal Vascular Reactivity at Various Stages of Deoxycorticosterone Hypertension in Rats

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SUMMARY We studied the possible contribution of increased vascular reactivity to the development of deoxycorticosterone acetate (DOCA) hypertension in rats. Changes in vascular reactivity were studied in isolated, constant-flow perfused kidneys of male Sprague-Dawley rats post unilateral nephrectomy which received a single subcutaneous implant of Silastic containing 100 mg/kg of DOCA and were given 0.9% NaCl plus 0.2% KCl solution to drink. Age- and sex-matched control rats (CR) received Silastic implants. The hypertensive rats were studied at 4 days (prehypertensive stage) and 61 days (chronic hypertensive stage) after implantation. At an average of 4 days, blood pressure in DOCA-treated rats did not differ significantly from that measured prior to implantation, and renal vascular resistance was similar to that in the matched controls. However, renal vascular reactivity to norepinephrine (NE), vasopressin (ADH), and angiotensin II (A II) was enhanced in the DOCA-treated rats. Dose-response curves for kidneys of these prehypertensive rats showed a parallel leftward shift, reduced ED₅₀, and decreased threshold dose. After an average period of 61 days, blood pressure in the DOCA-treated rats was 189.2 ± 3.5 mm Hg, and renal vascular resistance at maximal vasodilation was significantly greater ($P < 0.0001$) than in CR. Renovascular reactivity to NE, ADH, and A II was markedly enhanced. Dose-response curves were characterized by a leftward shift, steeper slopes, increased maximal responses, decreased ED₅₀, and threshold doses. Hence, enhanced vascular reactivity clearly precedes and may initiate the rise in arterial pressure in DOCA-treated rats. The initial increase in response to vasoconstrictor substances is attributed to an enhanced sensitivity of vascular smooth muscle, whereas, in the chronic stage of hypertension, structural changes in the resistance vessels, secondary to the rise in arterial pressure, are the main mechanisms responsible for the intensified reactivity. *Circ Res* **46**: 619-624, 1980

INCREASED vascular reactivity to pressor agents is considered a primary characteristic of chronic deoxycorticosterone acetate (DOCA) hypertension in the rat (Finch and Haeusler, 1974; Beilin et al., 1970). Recently, longitudinal studies of changes in whole-body vascular reactivity in the DOCA-hy-

pertensive pig revealed an enhanced reactivity prior to a significant rise in arterial pressure (Berecek and Bohr, 1978). This finding suggested that the increase in vascular reactivity participates in the development of DOCA hypertension.

In the current study, the temporal relationship between the development of hypertension and the appearance of changes in vascular reactivity was studied in isolated, perfused kidneys of DOCA-hypertensive rats. The use of such a preparation, devoid of extrinsic neural and humoral control, permits a more direct analysis of alterations in the responses of the resistance vessels. The animals

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were studied at an early stage (average 4 days) and at a late stage (average 61 days) after DOCA implantation, corresponding to the prehypertensive and chronic stages of hypertension, respectively. The purpose was to characterize changes in vascular reactivity over time and to determine whether an increased reactivity to pressor agents could be a primary pathogenic mechanism underlying DOCA hypertension in the rat.

Methods

Experimental Animals

All studies were carried out on male Sprague-Dawley rats, housed individually in Macrolon cages and fed a standard laboratory chow (Ssniff) containing Na^+ , 100 mEq/kg, and K^+ , 100 mEq/kg. At the beginning of the experiment, the animals weighed 150–190 g. In all animals, a left nephrectomy was performed under ether anesthesia. The experimental rats received subcutaneous implants of Silastic strips (silicone rubber, Dow-Corning Co.) impregnated with deoxycorticosterone acetate (DOCA, Sigma Chemical Co.), the dose being 100 mg/kg. The control animals received Silastic implants without DOCA. Drinking fluid contained 0.9% NaCl and 0.2% KCl. Initially, 10 control rats (CR) and 10 DOCA rats (DR) were observed for 8 weeks after implantation to characterize the course of development of hypertension. Systolic blood pressure was measured, under light ether anesthesia, by means of tail plethysmography (Byrom and Wilson, 1938) on two occasions prior to, and then at weekly intervals after, implantation. In some of the experimental rats, pressures were recorded at 2-day intervals for the first 2 weeks after implantation. Renal perfusion was carried out at an average of 61 days (range: 35–95 days) after implantation.

An additional eight DR and eight CR were prepared as described above. In these rats, blood pressure was recorded on two occasions prior to and after DOCA or Silastic implantation. Kidney perfusion was carried out an average of 4 days (range: 3–5 days) after implantation.

Isolation and Perfusion of the Kidney

The rats were anesthetized with sodium pentobarbital (Nembutal, 50 mg/kg, ip). Surgical isolation and perfusion of the kidney were carried out according to a technique previously described by Hoffbauer et al. (1973) with the following modifications: (1) the right kidney was perfused through a catheter placed into the distal aorta and advanced to the origin of the right renal artery, and (2) the kidneys were perfused at constant flow with a modified Krebs-Henseleit solution containing Ficoll 70 (Pharmacia AB), 35 g/liter, as colloid.

The pH of the perfusate was 7.4; it was maintained at a temperature of 37°C and gassed with 95% O_2 and 5% CO_2 . Perfusion pressure was re-

corded continuously using a pressure transducer (Statham P23Db), and perfusate flow was recorded continuously via a drop counter placed at the venous catheter. All results were recorded on a Sanborn polygraph (Hewlett-Packard, model 7702B). An equilibration period of 60 minutes were allowed before the experimental protocol was begun.

Experimental Protocol

Vasoconstrictors employed in the reactivity studies were the following: norepinephrine (Arterenol, Hoechst), vasopressin (Pitressin, Parke-Davis), and angiotensin II (Hypertension, CIBA). The doses of all drugs are expressed as base.

Perfusion flow was approximately 5.5 ml/g per min. At this flow, the renal vascular bed was found to be atonic, as bolus injections of papaverine HCl (Roche) into the arterial bed produced no further fall in perfusion pressure. Baseline perfusion was stable for the duration of the experiment (140–160 minutes). After the equilibration period, cumulative dose-response curves to the vasoconstrictors were obtained in the following order: norepinephrine, vasopressin, and angiotensin II. A period of 20 minutes was allowed between each drug administration. Doses of the drugs were applied in bolus injections from subthreshold to maximum doses. All injections were in 10- μl volumes and applied intra-arterially through a multiple puncture site close to the renal artery cannula.

Statistical Methods

All values presented in the text and in the figures are means \pm SE. Student's *t*-test was used to evaluate the significance of the differences between DOCA-treated rats studied at the prehypertensive and chronic stage and their respective controls. A one-way analysis of variance among the weekly measurements of arterial pressure was used to determine the pattern of development and course of hypertension with DOCA + salt treatment. When a significant ($P < 0.05$) *F*-ratio was obtained, the Newman-Keuls test was used to determine at which time periods the arterial pressure was significantly different from pretreatment measures.

Results

Rats, post unilateral nephrectomy, implanted with DOCA and given 0.9% saline as drinking fluid, rapidly developed hypertension (Table 1). Seven days after DOCA implantation, the blood pressure increase was not yet significant, but later, it rose to a plateau of 180 mm Hg after the 4th week. No change in arterial pressure over a comparable period of time was noted in the control rats.

Changes in Renal Vascular Reactivity

In the prehypertensive stage, the blood pressure of the DOCA-implanted rats did not differ from that of the control rats (117 ± 3.2 mm Hg vs. 116.0

TABLE 1 Development of DOCA Hypertension in the Rat

		Post-DOCA					
	Pre-DOCA	1 wk	2 wks	3 wks	4 wks	5 wks	8 wks
DOCA rats (<i>n</i> = 10)							
Mean systolic blood pressure (mm Hg)	112.2	119.0	141.6*	165.5*	178.9*	179.4*	181.2*
SE	3.1	2.6	4.6	4.7	5.3	5.0	4.1
Mean body weight (g)	193.4	221.8	254.1	270.0	283.0	306.0	367.0
SE	3.3	4.6	6.2	5.3	5.7	6.5	21.0
		Post-Silastic					
	Pre-Silastic	1 wk	2 wks	3 wks	4 wks	5 wks	8 wks
Control rats (<i>n</i> = 10)							
Mean systolic blood pressure (mm Hg)	110.6	115.2	118.5	111.2	112.4	107.8	116.3
SE	3.8	3.0	4.0	2.9	2.4	2.1	2.4
Mean body weight (g)	189.7	222.5	249.6	270.4	289.0	314.0	403.0
SE	5.0	4.5	5.7	7.1	5.6	8.7	13.0

Data are presented as group mean \pm SE. * $P < 0.005$, determined by one-way analysis of variance and the Newman-Keuls test.

± 2.9 mm Hg, respectively, Table 2). Renal vascular resistance also was similar in both groups of rats (Table 2), but reactivity to norepinephrine, vasopressin, and angiotensin II was increased in renal vascular beds of DOCA-treated rats as compared to control rats (Figs. 1–3). Dose-response curves were characterized by a parallel shift to the left without any change in the slopes of the curves (Table 3). Furthermore, threshold doses as well as ED_{50} for the three pressor agents were significantly lower in the DOCA-treated rats.

In rats with established hypertension (Table 2), the baseline renal vascular resistance was significantly higher than in the normotensive control rats. Vascular reactivity to the three pressor agents was enhanced (Figs. 1–3). In contrast to the kidneys of rats in the prehypertensive stage or the age-matched control rats, the dose-response curves showed a substantially higher maximum response and, consequently, were shifted to the left in a nonparallel manner. The curves obtained from kid-

neys of the chronic DOCA-hypertensive rats had steeper slopes than those of kidneys from the control rats or those of rats in the prehypertensive stage (Table 3). Moreover, threshold doses and ED_{50} were significantly reduced (Table 3).

Discussion

These studies demonstrate that increased reactivity in renal vascular beds of rats treated with DOCA and salt after unilateral nephrectomy clearly precedes the development of hypertension. The increase in reactivity in the prehypertensive stage appears to be attributable to alterations in the sensitivity of the vascular smooth muscle cells to various pressor agents. In our preparation, this is obvious from the decrease in threshold to stimulation and in ED_{50} , as well as from the parallel leftward shift in the dose-response curves for all three vasoconstrictors. The further enhancement of vascular reactivity in the chronic stage of DOCA hy-

TABLE 2 Characteristics of the Experimental Rats at Perfusion

Group	Weight (g)	Systolic blood pressure (mm Hg)	Renal perfusion pressure (mm Hg)	Renal perfusate flow (ml/g per min)	Renal vascular resistance (mm Hg/ml per g per min)
DOCA-salt prehypertensive* (n = 8)	200.0 \pm 9.8	117.1 \pm 3.2	39.7 \pm 1.3	5.6 \pm 1.8	7.1 \pm 0.25
Control-salt* (n = 8)	177.5 \pm 14.1	116.0 \pm 2.9	40.9 \pm 2.8	5.9 \pm 0.19	6.9 \pm 0.42
DOCA-salt† chronic (n = 8)	387.5 \pm 18	189.2 \pm 3.5	53.8 \pm 4.8	5.3 \pm 0.15	10.1 \pm 0.69
Control-salt†	425.0 \pm 10	113.3 \pm 5.2‡	37.0 \pm 1.7§	5.5 \pm 0.14	6.7 \pm 0.24‡

Responses are expressed as group mean \pm SE.

* DOCA and control rats perfused 4.0 ± 0.32 days postimplantation.

† DOCA and control rats perfused 61 ± 6.0 days postimplantation.

‡ $P < 0.0001$ compared to DOCA-salt (Student's *t*-test).

§ $P < 0.005$ compared to DOCA-salt (Student's *t*-test).

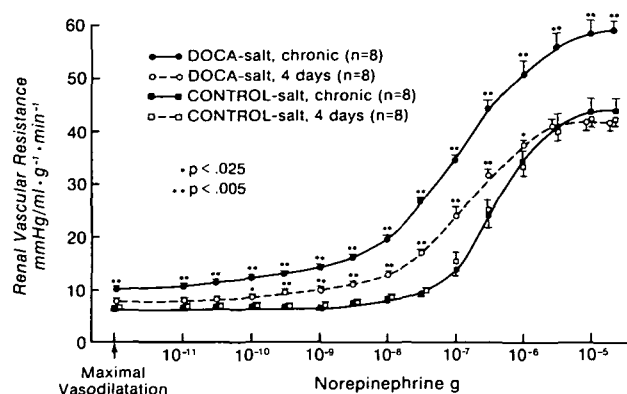


FIGURE 1 Dose-response curves in isolated, perfused kidneys from rats with DOCA-salt hypertension in the prehypertensive state (4 days after implantation of DOCA) and the chronic hypertensive stage (61 days after implantation). Response (ordinate) is given as renal vascular resistance (mm Hg/ml per g per min) which was calculated as the quotient of the recorded perfusion pressure (mm Hg) divided by the constant perfusate flow (ml/g per min). Responses are expressed as mean \pm SE. Significant differences from control, determined by Student's *t*-test, are indicated by asterisks (*); *n* = number of animals in each group; abscissa = dose of norepinephrine (g/100 μ l injection volume).

pertension is considered to be a consequence of structural changes in the resistance vessels secondary to the rise in arterial pressure. In vascular beds of chronically hypertensive rats, a greater resistance was obtained at maximal vasodilation, and the dose-response curves showed steeper slopes and greater maximum responses than those from vascular beds of the age-matched control rats. These findings give functional evidence for a structural alteration (increased medial thickness) of the resistance vessels (Folkow et al., 1970). Our study in the kidney and other studies on isolated artificially perfused vascular preparations (Finch and Haeusler, 1974) or in isolated arterial strips (Holloway and Bohr, 1973;

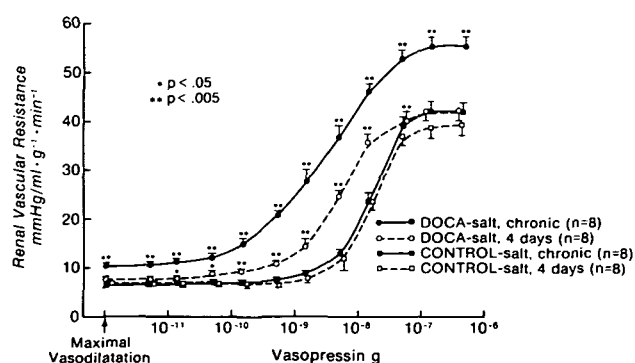


FIGURE 2 Dose-response curves of the same kidneys as in Figure 1 to vasopressin. Ordinate as in Figure 1; abscissa = dose of vasopressin (g/100 μ l injection volume).

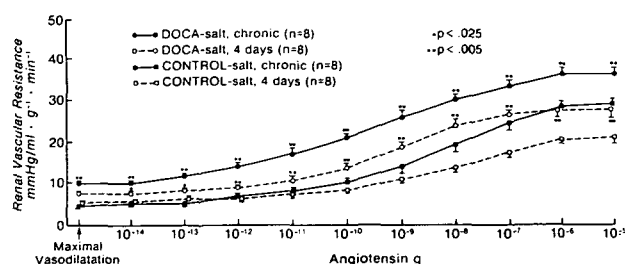


FIGURE 3 Dose-response curves of the same kidneys as in Figure 1; abscissa = dose of angiotensin II (g/100 μ l injection volume).

Hansen and Bohr, 1975) show that alterations in reactivity persist in preparations devoid of humoral and neurogenic control. Therefore, it can be concluded that an intrinsic change occurs in the vascular smooth muscle resulting in enhanced sensitivity to external stimuli.

Prior to chronological studies of vascular reactivity in DOCA hypertension, it had been demonstrated that changes in smooth muscle sensitivity were independent of the rise in arterial pressure (Hansen and Bohr, 1975; Berecek and Bohr, 1977; Finch, 1975). Hansen and Bohr (1975) kept one hindlimb of DOCA-hypertensive rats at a normotensive pressure through arterial ligation and found that increased sensitivity also developed in the protected vascular bed. Similar findings were obtained in the DOCA-hypertensive pig also using arterial ligation (Berecek and Bohr, 1977). Furthermore, Finch (1975) found that increased responsiveness of perfused mesenteric arteries persisted in DOCA-hypertensive rats whose blood pressure had been substantially lowered by antihypertensive drug therapy.

Changes in vascular reactivity prior to the rise in arterial pressure have been reported in some models of experimental hypertension (McQueen, 1956; Ogden et al., 1940) and in humans (Doyle and Fraser, 1961). In pigs with DOCA implants, an increased vascular sensitivity was observed as early as 2 days after implantation, before a significant rise in arterial pressure (Berecek and Bohr, 1978). In studies of ion fluxes, Jones and Hart (1975) demonstrated a significant increase in ion turnover which preceded the rise in arterial pressure in aortas from DOCA-hypertensive rats.

Possible mechanisms underlying the increased vascular sensitivity and the rise in blood pressure in DOCA hypertension include the following: (1) direct or indirect myogenic effect of DOCA, (2) altered central and peripheral neurogenic influence, (3) increased secretion of vasopressin, and (4) increased intracellular sodium concentration. Studies concerning the direct action of DOCA are few in number, and the data are conflicting. Evidence has been given that DOCA potentiates the vascular response to catecholamines in vivo (Beilin et al., 1970) and in vitro (Kalsner, 1969). Kalsner (1969),

TABLE 3 Dose-Response Curve Slopes* and ED₅₀ to the Agonists for DOCA-Hypertensive and Control Rat Kidneys

Group	Norepinephrine		Vasopressin		Angiotensin II	
	ED ₅₀ (10 ⁻⁸ g)	Slope	ED ₅₀ (10 ⁻⁹ g)	Slope	ED ₅₀ (10 ⁻⁹ g)	Slope
DOCA-salt prehypertensive (n = 8)	4.3 ± 0.66	6.03 ± 0.57	2.44 ± 0.57	7.0 ± 0.81	0.73 ± 0.19	2.1 ± 0.30
Control-salt (n = 8)	18.7 ± 4.2‡	5.67 ± 0.31	10.0 ± 1.09§	6.58 ± 0.38	14.6 ± 4.0‡	1.14 ± 0.15
DOCA-salt chronic (n = 8)	2.21 ± 0.58	7.48 ± 0.35	0.93 ± 0.26	8.91 ± 0.37	0.42 ± 0.15	2.03 ± 0.14
Control-salt chronic (n = 8)	24.7 ± 0.63‡	5.61 ± 0.55†	9.86 ± 1.27§	6.0 ± 0.38‡	10.8 ± 4.5	1.51 ± 0.20†

Data are presented as mean ± SE.

* Dose-response curve slope, derived from linear regression, is given as the change in renal vascular resistance (mm Hg/ml per g per min) per 10-fold increase in drug dose.

† $P < 0.01$; ‡ $P < 0.005$; § $P < 0.0001$; || $P < 0.025$. Compared to DOCA-salt (Student's *t*-test)

studying rabbit aortas, has shown that DOCA potentiated the response of this tissue to catecholamines through an inhibition of the enzyme catechol-*o*-methyltransferase. However, the rabbit does not develop hypertension under the influence of DOCA and salt (Gross and Schmidt, 1958). Recently, it has been shown that, in contrast to its effect on reactivity in rabbits, DOCA produced a depression in contractile response to catecholamines and other vasoactive agents in arteries of rats (Koehler et al., 1979).

It has been suggested that enhanced activity of the peripheral nervous system (deChamplain, 1973) owing to a central mechanism (Haeusler et al., 1972), contributes to the development and maintenance of DOCA hypertension. There appears to be a defect in the retention and storage of norepinephrine in postganglionic sympathetic fibers, which occurs prior to the rise in arterial pressure and results in an increased release of norepinephrine (deChamplain, 1973). Jones (1973) has shown that norepinephrine increases K⁺ turnover in the vascular smooth muscle cell in a dose-dependent manner. Moreover, in recent studies of the relationship between norepinephrine and K⁺ turnover in arteries from DOCA-hypertensive rats, the turnover in response to norepinephrine was significantly greater than that found in control rats (Jones et al., 1977). These findings suggest a cellular basis for the hypersensitivity to norepinephrine. A shift in the dose-response relationship between norepinephrine and K⁺ turnover could produce greater depolarization of the smooth muscle membrane resulting in increased contractile activity for a given level of norepinephrine. When the role of the sympathetic nervous system in the development of these cellular changes was assessed, it was found that an intact sympathetic nervous system was not a requirement for either the increased turnover of K⁺ or the increased responsiveness to norepinephrine (Jones et al., 1977). Thus, it appears from these findings and our own that intrinsic changes occurring in the vascular smooth muscle cell are nonspecific and are a result of the DOCA-salt treatment, rather than the consequence of an alteration in neural activity.

Vasopressin may also play a role in DOCA hypertension, since it has been shown that plasma vasopressin was increased in DOCA-hypertensive rats (Möhring, 1978). Moreover, a marked increase in the sensitivity of the DOCA-hypertensive rats to the vasoconstrictor effects of vasopressin was found. Vasopressin has been shown to be a more potent vasoconstrictor of resistance vessels than angiotensin II, and these vessels respond to doses of vasopressin in the physiological range (Altura and Altura, 1977). Furthermore, there is evidence that subpressor doses of vasopressin modify the cardiovascular actions of catecholamines and potentiate catecholamine-induced contraction in the microvasculature (Bartelstone and Nasmyth, 1965). No studies have been done, as yet, to determine the role of vasopressin in the prehypertensive stage. The exact action of vasopressin on vascular smooth muscle and how it potentiates the response to catecholamines also are not known. Current evidence suggests that changes in vasopressin sensitivity may be a secondary result of the primary, nonspecific increase in the sensitivity of vascular smooth muscle.

The ability of DOCA to produce hypertension has been shown to depend directly on sodium supply (deChamplain, 1973). Moreover, the retention and storage of norepinephrine (deChamplain, 1973), as well as the increase in vascular reactivity (Aboud, 1974), depend on sodium intake. The observation that a low sodium diet corrects the dysfunction of the nervous system while simultaneously rendering the DOCA-treated rats normotensive lends strong support for the role of sodium in DOCA hypertension. The sodium ion has a direct effect on many facets of vascular smooth muscle cell function. Increased intracellular concentration of sodium may decrease the resting membrane potential of the smooth muscle cell, and this, in turn, could underlie increased reactivity of the cell to vasoactive drugs, particularly those with depolarizing actions (Bulbring, 1962). Furthermore, changes in membrane potential brought about by changes in membrane permeability to K⁺, Na⁺, and Cl⁻ and the concentration gradients of these ions across the

cell membrane may have effects on calcium handling by the cell. Calcium may be released either from stores in the sarcoplasmic reticulum or by influx of the ion through the surface membrane (Jones, 1974). Recent studies have supported a direct sodium-calcium counterexchange system with sodium concentration gradients influencing the movement of calcium across the smooth muscle membrane (Blaustein, 1977). It has been postulated that an increase in intracellular sodium would decrease the transport of calcium out of the cell, increasing the concentration of active calcium within the cell, and thereby, increase the responsiveness of the cell to a variety of stimuli. There is, however, limited evidence for an actual alteration in the intracellular concentration of sodium in the vascular smooth muscle cell during experimental hypertension. In isotopic studies of ion flux in arteries from DOCA-hypertensive rats (Jones, 1976), it was found that there was an increased turnover of K^+ and Cl^- and an excess accumulation of Na^+ as compared to controls, suggesting that the membrane permeability to all three ions is increased. Increase in the passive permeability of smooth muscle from DOCA rats was substantiated by Friedman (1974), using ion exchange methods. Evidence also has been given that alterations in active transport of ions across the plasma membrane of vascular smooth muscle from hypertensive animals occur, although it has not been resolved whether Na^+-K^+ ATPase activity is increased (Friedman and Nakashima, 1978) or decreased (Pamnani et al., 1978) in DOCA hypertension. The evidence that alterations in vascular smooth muscle membrane permeability and ion turnover occur prior to the rise in arterial pressure (Jones and Hart, 1975) suggests that these changes may underlie increased vascular reactivity and the rise in blood pressure in DOCA hypertension.

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