Vascular Reactivity of Rats and Dogs Treated with Desoxycorticosterone Acetate.*† (17705)

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Hypertension and vascular disease can be readily reproduced in rats treated with desoxycorticosterone acetate (DCA) under suitable conditions(1,2). One possible extrarenal mechanism of this hypertension is increase in pressor responsiveness of the vascular tree to agents such as renin, angiotonin and epinephrine. On the other hand, DCA-hypertension of any considerable degree has not been obtained in dogs(3,4). Therefore to assess the contribution of pressor hyperresponsiveness to DCA hypertension we have compared the vascular reactivity of control and DCA-treated rats and dogs.

Methods. In the first series of experiments, 21 male albino rats weighing 217 g were divided into 2 groups following unilateral nephrectomy. Animals of Group I received 2 subcutaneous implants of 40 mg pellets of DCA while those of Group II were kept as untreated controls. All the rats were maintained on a high sodium ration by giving 1% saline solution as drinking water. Starting on the 11th day, animals were tested for vascular reactivity to epinephrine, renin and angiotonin. To eliminate any possible variation due to the dilution of these drugs, 1 control was always run simultaneously with 1 or more experimental animals. Following nembutal anesthesia (30 mg per kilo) and heparinization, the carotid artery was cannulated and connected to a mercury manometer. Injections were made into the femoral vein. The dose of each substance was kept constant throughout the experiment and consisted of 0.1 cc (0.125 γ) of epinephrine, 0.1 cc of renin and 0.2 cc of angiotonin. The stock renin, prepared by Dr. Arda Green, contained 30 mg of protein per cc; 0.1 cc gave a 35 mm Hg rise in a dog under pentobarbital anesthesia. Before use, it was diluted in the proportion of 1 part in 10 physiological saline. Angiotonin, prepared according to the method of Page and Helmer(5) as modified by Plentl and Page(6) contained 10 units per cc and was injected as such.

In the second series of experiments we used 3 mongrel dogs weighing 10 to 20 kg. They were unilaterally nephrectomized, given 1% saline to drink and then were treated with DCA in the form of a water suspension, injected subcutaneously once every 4 days in a dose of 100 mg. Animals were tested before uninephrectomy, after uninephrectomy and after treatment with 500 mg of DCA. During treatment with DCA their daily water intake ranged from 3.5 to 4 liters as saline compared with 500 to 700 cc after operation but before treatment. Vascular reactivity was determined under nembutal anesthesia (35 mg/kg intraperitoneally) by the method described by Page and Taylor(2). The doses of the various drugs were epinephrine 0.1 cc of a 1/20,000 dilution, nor-adrenaline 10 γ angiotonin 5 units in 0.5 cc, veratrum alkaloid 29 γ in 0.3 cc, sodium azide 125 γ in 0.1 cc and tetraethylammonium chloride 5

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TABLE I.

Differences in mm Hg Between Pressor Responses of Control and of DCA-Treated Rats to Epinephrine, Renin, and Angiotonin.

	1*	2*	3	4	5	6	7	8	9	10	11	12	Avg
Epinephrine	+1	−4	+9	−1.5	+13	+17.5	+4	+8	+5	+5	+18	−10	+5.4
Renin	+10	−3	+18	−4	+7	+3	+17	+19	+21	−20	+19	+14	+8.4
Angiotonin	—	+1	+14	−7	+6.5	+2.5	+10	+4	+6	−9	−3	+16	+3.3
Duration of DCA treatment (days)	8	9	22	32	33	33	34	51	51	52	53	54	
Blood pressure difference between control and DCA rats	30	20	22	74	60	58	43	56	74	84	48	80	

* These rats received 0.1 *cc* of angiotonin.

TABLE II.

Average Vascular Responses of Dogs to Various Drugs.

	Epinephrine	Nor-adrenalin	Angiotonin	Veratrum alkaloid	Sodium azide	Tetraethyl ammonium
Before nephrectomy	+12	+54	+28	−38	−40	−44
After "	+17	+54	+25	−40	−48	−52
" DCA treatment	+15	+50	+22	−21	−38	−34

mg/kg body weight (Etamon: Parke, Davis and Co.).

Results. Although the same rat gave a relatively constant response to repeated injections of the same dose of epinephrine and angiotonin, there were large variations from animal to animal. In the control group, responses to epinephrine varied from −8 to +15.5 mm Hg, to renin from +11 to +50 mm Hg, and, to angiotonin from +15 to +27 mm Hg. The same group variability occurred in the DCA treated rats: responses to epinephrine varied from +3 to +25 mm Hg, to renin from +15 to +54 mm Hg and to angiotonin from +11 to +34 mm Hg. The response was independent of the duration of treatment and of the degree of hypertension. Since values of the 2 groups overlap each other, we decided that the difference in response to a given drug in the control and simultaneously injected experimental rat would give a clearer picture of the results. In Table I we list these, the duration of treatment and the differences between the blood pressure of control and experimental rats. All the treated rats had an elevated blood pressure; furthermore, all except rats 1, 2 and 3, had vascular lesions of pan- or polyarteritis. These pathologic vascular changes caused by DCA have been described elsewhere in detail(8).

Table I shows, horizontally, the wide variations of response to each drug of treated animals as compared to each other, and, vertically the heterogeneity of responsiveness as between drugs in the same test subjects. Rat No. 12 is hypersensitive to renin and angiotonin and hyposensitive to epinephrine, while the reverse is true in rat No. 10. The blood pressure levels of these 2 rats were the same. Averages in the last column indicate that there is only slight increase in the sensitivity of hypertensive animals.

The results obtained in dogs are summarized in Table II. As expected, uninephrectomy did not have any consistent influence on the vascular response. Therefore, if we accept as normal the variations between the responses

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obtained before and after nephrectomy, one can conclude that DCA did not change the vascular reactivity. It should be pointed out that none of the dogs showed a significant increase in blood pressure as a result of DCA treatment. Blood pressure values obtained regularly by femoral intra-arterial puncture averaged 125 mm Hg (114-148) before and 138 mm Hg (124-150) after treatment. In no instance was there even a consistent trend of blood pressure change as a result of DCA. This is in accord with previous observations that normal dogs are resistant to DCA hypertension(3,4).

It has already been shown that hypertension elicited in dogs by silk perinephritis does not influence the vascular response to various chemical stimuli(7,9). From the present paper the same conclusion applies to DCA treated dogs. Although we found that the average responses to epinephrine, renin and angiotonin were slightly greater in DCA treated than in control rats, it is unlikely that they are significant since many hypertensive rats showed a normal or a subnormal vascular sensitivity. Furthermore, such slight differences would not be sufficient to explain persistent hypertension. The present data do not support the view that part of the pathogenesis of DCA hypertension in the rat can be explained on the basis of a functional hyper-activity of the vascular system(10).

Summary. Chronic treatment with DCA of dogs and rats, does not increase significantly vascular response to epinephrine, renin and angiotonin to explain DCA-hypertension on the basis of vascular hypersensitivity.

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Depression of Tracer Ion Uptake Curve in Rat Erythrocytes Following Total Body X-Irradiation. (17706)

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Radioactive iron given enterally or parenterally has been shown by Hahn and co-workers(1) to be incorporated into the red blood cell as an integral part of the hemoglobin molecule. In addition, an *in vitro* experiment has demonstrated the failure of radio iron introduced into the plasma to exchange with hemoglobin iron of the mature erythrocyte(2). In contrast, more recent work by Walsh *et al.*(3) indicates the ability of circulating reticulocytes to accumulate radio iron ***in vitro*** to a small extent. Thus it appears that radio iron found in circulating erythrocytes is present principally in cells that have been released from bone marrow following the administration of the tracer dose of iron. Morphologic evidence that the erythropoietic tissue of bone marrow is extremely sensitive has been provided by Bloom and Bloom(4) who found that erythroblasts disappeared from the bone marrow of rats earlier than the myeloblasts following a half lethal dose of X-rays. That this degree of radiosensitivity is compatible with the apparently contradictory findings of normal quantities of circulating erythrocytes is entirely credible when, as has been pointed out by several authors, the longevity of these

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