Potassium Chloride Flooding and DCA-induced Cardio-renal Hypertrophy in the Rat. (18500)

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Desoxycorticosterone acetate (DCA) overdosage under suitable conditions induces cardiac and renal hypertrophy(1,2), adrenal atrophy(3), and periarteritis nodosa(1,4). Simultaneous treatment of rats on DCA-overdose with certain "acidifying" salts prevents these signs of cardiovascular damage, whereas similar treatment with potassium chloride does not(4). Similar KCl treatment to DCA-treated rats does not prevent the hypertension (5), or renal hypertrophy following DCA-overdosage(6). Subsequent work indicated that a dietary excess of potassium chloride leads to a decrease of cardiac mass, an increase of renal mass, and signs of adrenal glomerular zone hyperactivity; these changes are reversible(7).

This paper reports data which indicate that dietary excess of KCl to DCA-treated rats prevents the cardiac and adrenal changes characteristic of the overdosage, without altering the effect on the kidney.

Materials and methods. Four groups of female Wistar rats were treated as follows: Group I rats received single subcutaneous implants of 50 mg DCA, (Percorten, crystalline, Ciba), in gelatin capsules and were maintained on Purina Laboratory Chow and a 0.2% NaCl solution as the sole source of fluid. The NaCl was added in order to sensitize the animals to the effects of DCA; Group II rats received similar implants of DCA and were maintained as Group I rats except that their fluid supply contained 0.2% NaCl and 2% KCl. Group III rats were given implants of empty gelatin capsules and were maintained as those of Group II. Rats of Group IV served as controls and were kept on Chow and tap water (or 0.2% NaCl). Four of this group were given 0.2% NaCl; this solution produced no discernible effects on the animals. All animals were killed at the end of 30-32 days. The heart and kidneys were weighed; the hearts were kept for histological studies. One adrenal from each animal was used for the histochemical detection of cholesterol, the other for ascorbic acid, after methods used in another study(3).

Results. The final body weights of the 4 groups of rats were similar (200 g), therefore the absolute organ weights are presented. The mean heart weight of DCA-treated (Group I) rats is significantly greater, whereas the mean heart weight of KCl-treated (Group III) rats is significantly lower, than that of control animals. The mean heart weight of rats receiving DCA-KCl (Group II) is not different from control heart weight. Comparison of the observed heart weights with heart weights predicted from standard data(8) shows a similar pattern, that is, DCA increases, KCl decreases, heart weight, while DCA-KCl does not alter heart weight from normal range (Table I). Rats of groups I and II show kidney weights significantly greater than those of control animals. In this study as in a previous one, the observed kidney weights are much higher than the predicted weights. KCl was reported in a previous paper to induce an increase of renal mass(7).

The increase of heart weight observed in

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TABLE I. Data on Rats Under DCA, KCl, and DCA-KCl.

Treatments Group and No. rats	DCA-S* I (8)	DCA-KCl-S II (8)	KCl-S III (8)	None (4 on S) IV (8)
Heart wt: mg ± S.E.†	756 20	636 10	577 15	669 12
Dev. from prediction‡	+13%	— 4%	—14%	0%
Kidney wt: g ± S.E.	1.87 0.05	1.83 0.07	1.76 0.07	1.73 0.02
Dev. from prediction‡	+48%	+45%	+40%	+36%
Mesenteric periarteritis nodosa	5	0	0	0

* All animals were sensitized with 0.02% NaCl, excepting 4 of group IV.

† S.E. $= \sqrt{\frac{\Sigma (x-x')^2}{n(n-1)}}$. x' = mean value of x.

‡ Heart and kidney weights predicted from the data of Addis and Gray(8).

group I animals was due to ventricular hypertrophy (ascertained by histological study), was not due to increased water content (unpublished data), and was associated with mesenteric periarteritis nodosa in 5 of the 8 animals of the group. Periarteritis nodosa was not observed in any other area, or in any other group of animals in this study. Signs of glomerular zone hyperactivity of the adrenal, widening of the zone, hypertrophy of the cells, increased cholesterol content ("resistance phase")(?), associated with peripheral aggregation of ascorbic acid in many of the cells, occurred in the animals flooded with KCl. Glomerular zone atrophy, disappearance of its cholesterol, and subcapsular clumping of ascorbic acid, all signs of underactivity, were observed in the adrenals of Group I rats (DCA). The adrenals of the DCA-KCl (Group II) animals were of normal appearance except for disappearance of the transitional zone. Indeed this zone is very plastic even under normal conditions and its disappearance is probably of no significance.

Discussion. The data indicate that rats sensitized with NaCl and on DCA overdose develop cardiac hypertrophy and mesenteric periarteritis nodosa. This response was observed in previous instances(1,4,9) and was referred to the sodium retaining action of DCA. It has also been suggested that a normal balance exists between the amount of DCA-like corticoids in the body and the active renal mass(10); under this mechanism an excess of DCA supply to the animal disturbs this balance and elicits changes referable to the "non-inactivated" DCA, that is, cardiac hypertrophy, periarteritis nodosa and hypertension. A similar pattern of events may follow diminution of renal mass in which case even endogenous DCA-like corticoids may elicit the cardiovascular changes.

The observation that simultaneous KCl flooding prevented the signs of cardiac toxicity of DCA may be explained on the basis of either theory. The electrolyte could conceivably lead to sodium diuresis and in this manner depress the damaging effects of DCA. On the other hand, the excess KCl supply, through an increased need for the potassium eliminative function of corticoids, could have led to an increased "utilization" of DCA. With reference to the latter mechanism is the observation that the adrenal hyperactivity induced by KCl flooding is prevented by simultaneous DCA treatment. In other words, in KCl flooding, the adrenal responded by producing an increased amount of potassium chloride-depleting hormones, but this compensatory reaction did not occur in the presence of a high exogenous supply of DCA.

It is possible that the kidney participated in the changes observed in this study, but the exact nature of its participation is not known. Kidney hypertrophy was associated on the one hand with cardiac hypertrophy, periarteritis nodosa, and adrenal atrophy, and on the other hand with adrenal hypertrophy and a decrease of cardiac mass. Further studies are being conducted on the possible role of the kidney in these responses.

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Summary. The action of potassium chloride flooding on the cardiac, renal and adrenal effects of DCA-overdosage was investigated. The data indicate that there is a mutual antagonism between the actions of DCA and KCl on the heart and the adrenal. The role of the kidney in this antagonism is not known.

The author acknowledges the helpful interest shown by Dr. C. E. Leese. The DCA (Percorten, Ciba) was supplied through the generosity of Dr. F. E. Houghton, Ciba Pharmaceuticals, Inc., Summit, N. J.

Received January 29, 1951. P.S.E.B.M., 1951, v76.

Oral Administration of Vitamin B_{12} Containing Cobalt^{60} to Rats. (18501)

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Recent reports by Chow and associates (1,3) have demonstrated that when vit. B_{12} is administered orally to rats or humans, no microbiologic activity appears in the urine. They concluded from these observations that oral administration results either in the conjugation of vit. B_{12} to a form unavailable for the microorganism, in poor absorption in the intestinal tract, or in conversion to a form incapable of being excreted by the kidneys. Later they observed (unpublished work) that stool samples from rats receiving vit. B_{12} by mouth contained considerably more of this vitamin than stools excreted before administration. Although these data might be taken to indicate poor utilization of vit. B_{12}, this interpretation is complicated by the presence of some vit. B_{12} in the feces of untreated, normal rats and by the unreliability of the microbiologic assay for this vitamin in stool.

The availability of radioactive vit. B_{12} containing cobalt^{60} reported by Chaiet, Rosenblum and Woodbury(2) simplifies the analytical problem and permits a differentiation between the administered vitamin from that originally present, granting that the radioactivity due to cobalt^{60} found in the animal represents administered vit. B_{12}. It is therefore of interest to ascertain the distribution of vit. B_{12} as manifested by the presence of radioactive cobalt^{60} in urine and stool, as well as in certain organs of rats following oral administration. The results of such a study are reported below.

Experimental. Four normal rats weighing between 250 and 300 g were put into metabolism cages and fed a soy bean diet(3). Collections of urine and stool were made for 2 consecutive days. On the third day, 0.89 mg of radioactive B_{12},* with a specific activity of $\simeq 0.2$ microcurie per milligram, was administered orally to each rat. Daily collections of urine and fecal matter were again made for 3 to 4 consecutive days. On the fifth day after administration, the animals were sacrificed and the kidneys, liver, spleen, brain, testes and hearts removed. Each of these organs was homogenized *in toto* either with a Waring Blendor or with an Elvehjem homogenizer, and the suspensions were made up to a measured volume. An aliquot of each tissue homogenate was evaporated to dryness, wet ashed with H_2SO_4 after addition of several milligrams of ordinary cobalt to act

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* The radioactive vitamin employed in these experiments was provided by Merck & Co., Inc., on allocation by the Isotopes Division, U. S. Atomic Energy Commission.