Growth Effects of Desoxycorticosterone and Cortisone with Special Reference to Compensatory Renal Hypertrophy.* (19437)

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Ingle(1) and others(2,3) described the inhibitory effect which cortisone exerts on the growth of normal and abnormal tissues. It has been reported that doses of cortisone which inhibit body growth, fail to affect the size of the liver, testes, pituitary or heart in rats, although causing atrophy of the adrenals, thymus and spleen(4). Desoxycorticosterone, on the other hand, is known to produce enlargement of the kidneys and heart at certain dose levels(5), and atrophy of the adrenal cortex, primarily of the glomerulosa(6).

This study compares the activity of the two hormones with respect to certain growth effects, particularly the compensatory renal hypertrophy consequent to uninephrectomy. While these studies were in progress a communication appeared which presented data indicating that cortisone augmented compensatory renal hypertrophy(7). The methods of study employed differed from those used in the present instance, and may explain the differences in data and conclusions, as compared with those presented here.

Materials and methods. Sixty-eight female rats of the Holtzman strain, weighing 52-82 g were divided into 4 groups of similar average weight. One group received 1 mg of cortisone acetate† twice daily subcutaneously; the second group received desoxycorticosterone acetate (Doca) prepared in the same vehicle, in the same amount and manner as for cortisone; the third group was restricted as to food intake so as to cause the body weight to remain static as in the cortisone-treated animals; and the fourth group served as normal controls. Each group, except that on restricted feeding, consisted of 16 animals half of which were uninephrectomized at the beginning of the experiment. The group on restricted food intake consisted of 20 animals, 8 of which were uninephrectomized. Tap water was accessible to the animals at all times and Purina Laboratory Chow was fed in limited amounts to the group on restricted food intake and *ad lib.* to all other groups. The left kidneys, removed on the first experimental day from the animals in which compensatory renal hypertrophy was to be studied, were placed in Bouin's fixative for 24 hours, washed in water and weighed after careful drying on filter paper. The experiment was terminated on the 15th day and organs to be weighed were treated in the same manner as the kidneys removed at operation.

Results. The body and organ weights, together with their standard errors, are given in Table I, with other essential data.

Growth. Growth, as judged by increment in body weight, failed to occur in rats treated with cortisone and in the untreated animals on a restricted food intake. Doca neither accelerated nor retarded growth; these animals, and the controls, almost doubled their initial weight during the experiment.

Adrenals. The adrenal glands in the animals on a restricted food intake were, in proportion to their body weight, as large as those of controls. It would appear that the degree of food restriction employed did not evoke a stress response. In agreement with previously published results a slight degree of adrenal atrophy was produced by Doca and a more marked atrophy by cortisone.

Heart. The auricles were dissected from the hearts and the ventricles weighed. These were heavier, when the weight was expressed as a function of body weight, in cortisone-treated rats than in controls. In the remaining groups the heart weight was essentially the same, being unaffected by Doca, restricted food intake or uninephrectomy.

Kidneys. The left kidneys removed at

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TABLE I. Effect of Doca, Cortisone and Food Restriction on Growth of Body, Heart, Adrenal and Kidney.

	Data	Controls	Doca	Cortisone	Restricted diet
No. rats		8	8	8	12
†Body wt. g	Initial	66 ± 2*	67 ± 1	67 ± 3	66 ± 2
	Final	114 ± 2	125 ± 3	66 ± 4	66 ± 1
Adrenals	mg	31.1 ± 1	23.9 ± 1.1	8.2 ± 0.4	17.7 ± 0.2
	mg %	27.4 ± 1.3	19.3 ± 1.2	12.5 ± 0.8	26.9 ± 0.8
Heart	mg	290 ± 13	335 ± 14	246 ± 14	177 ± 6
	mg %	254 ± 7	268 ± 7	370 ± 15	268 ± 9
Kidneys, Left	mg	465 ± 18	599 ± 24	396 ± 16	309 ± 12
	mg %	405 ± 13	479 ± 12	598 ± 14	468 ± 12
1. Right	mg	479 ± 20	647 ± 28	412 ± 15	331 ± 8
	mg %	420 ± 15	518 ± 14	628 ± 21	501 ± 9
Renal mass	mg %	825 ± 25	997 ± 24	1226 ± 36	969 ± 19
No. rats		8	8	8	8
‡Body wt. g	Initial	67 ± 3	68 ± 2	68 ± 3	72 ± 2
	Final	107 ± 4	111 ± 3	64 ± 2	70 ± 2
Adrenals	mg	29 ± 2	25.4 ± 0.7	9 ± 0.2	19.7 ± 1.3
	mg %	27.5 ± 2.1	23 ± 0.8	14.1 ± 0.7	28.2 ± 2.1
Heart	mg	321 ± 8	297 ± 12	331 ± 17	211 ± 8
	mg %	303 ± 12	269 ± 6	513 ± 15	301 ± 15
Kidneys, Left (a)	mg	320 ± 12	306 ± 10	319 ± 11	317 ± 9
	mg %	474 ± 15	451 ± 13	457 ± 19	453 ± 14
2. Right (b)	mg	714 ± 26	848 ± 40	587 ± 17	422 ± 8
	mg %	673 ± 20	762 ± 20	915 ± 23	601 ± 12
Hypertrophy % (c)		60	47	46	20
% Renal mass intact		82	66	75	62

* Means ± Standard errors. a = at operation. b = at autopsy. $c = \frac{2-1}{1}\%$. † = Intact.
‡ = Uninephrectomized.

operation ranged, in the 4 groups, from 306 to 320 mg with an average of 315 mg. Since this was based on the weight of 32 kidneys it may be taken as representative of the weight of left kidneys of the non-operated animals at the beginning of the experiment. Therefore, the left kidneys of the intact animals averaged at the beginning 315 mg and attained a weight of 465 mg in controls; 309 mg in the restricted food group; 396 mg in cortisone-treated animals and 599 mg in Doca-treated animals. This represents an increase in actual renal mass of 47%, 0%, 25%, and 90% respectively. Kidney weight was greatest in proportion to body weight, in cortisone-treated rats, since the 25% increase in mass occurred in the absence of body growth. The degree of compensatory renal hypertrophy was calculated by subtracting the average weight of the right kidney (in mg/100 g body weight) of intact animals from the average weight of the right kidney of similarly treated uninephrectomized animals and expressing the difference in the latter as a percentage above the former. Compensatory hypertrophy was greatest in controls (60%), least in the group on restricted food intake (20%) and intermediate in the Doca (47%) and cortisone-treated rats (46%).

Discussion. In the group where body growth was held in abeyance by the restriction of food intake, kidneys of intact animals also failed to grow and the weights of the hearts and adrenals suggested that these organs grew little if at all. The proportionate suppression of growth resulted in a normal relationship between body size and the size of the visceral organs studied.

Although cortisone had the same effect on body weight as a restriction of food intake, the effect on the organ weights was quite different. The adrenals were atrophic, doubtless due to a suppression of adrenocorticotrophic hormone secretion, while the heart and kidney showed evidence of growth. In the case of uninephrectomized, cortisone-treated animals

the heart weight was greater even in absolute units than in any of the other groups. This effect may have been due to a moderate degree of hypertension, since cortisone is known to produce elevations of blood pressure under certain circumstances, especially in the presence of renal insufficiency(8). However, there is no proof that any animals were hypertensive in this experiment. Although the kidneys only increased their initial mass by 25% this occurred in the absence of any corporeal growth, resulting in great hypertrophy when kidney weight was expressed as a percentage of body weight. Desoxycorticosterone acetate augmented the growth of the kidneys and produced slight adrenal atrophy, but was without any effect on cardiac weight in the dose used.

Compensatory renal hypertrophy was greatest in control animals, amounting to 60%. The remaining kidney attained a weight which was 82% that of paired kidneys of intact rats. This was reduced to 46% (75% of total renal mass of intact rats) and 47% (66% total renal mass of intact rats) by cortisone and Doca respectively. Restriction of food intake which prevented renal growth in intact rats permitted a 20% hypertrophy (62% total renal mass) in uninephrectomized animals.

Apart from variations in animal size and hormone dosage, the most obvious dissimilarity between the present experiment indicating inhibition of compensatory renal hypertrophy by cortisone, and those suggesting an augmentation, is in the method of calculating hypertrophy. In the present study this was taken to be the weight difference between the remaining right kidney of uninephrectomized rats and the right kidney of similarly treated intact rats. Gross and Meier(7) took hypertrophy to be the difference in weight between the right kidney at the end of the experiment and the left kidney removed at the beginning. This figure includes in addition to compensatory hypertrophy, normal renal growth which would have occurred in this time had the rats remained intact, and fails to consider that this might have been affected by cortisone. The use of a group on restricted food intake in the present study permitted an evaluation of the degree to which organ weight changes in cortisone-treated animals might be due to impairment of body growth.

It is apparent from these and other studies that the anti-anabolic effect of cortisone does not affect all tissues equally, and hence its effect differs from the anti-anabolic effect of restricted feeding.

Summary. 1. In a dosage of 2 mg/day cortisone completely halted body growth and produced adrenal atrophy and slight cardiac hypertrophy. Kidney size in intact cortisone-treated rats increased by 25% which, since it occurred in the absence of an increase in body weight, resulted in kidneys which were disproportionately large in relation to body size. 2. Doca in the same dosage was without effect on body weight or heart weight. Slight adrenal atrophy and moderate enlargement of the kidneys in intact animals was observed. 3. Compensatory renal hypertrophy was greatest in controls and diminished to the same extent by either Doca or cortisone. It was suppressed to the greatest extent, but not completely prevented, by a restriction of food intake to a level permitting only maintenance of a static body weight.

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