COMPENSATORY HYPERTROPHY OF ONE ADRENAL GLAND IN RATS

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It is known that as early as 24 h after unilateral adrenalectomy the remaining adrenal increases in size. However, we do not know whether this increase is a compensatory hypertrophy, i.e., a hypertrophy in response to removal of the contralateral organ, or whether it is mainly due to stress. Neither do we know how long the process of compensatory hypertrophy continues, and it remains to be found whether all zones of the cortex take part in the hypertrophy [3, 4], or only some of them.

It has frequently been shown that the mitotic activity of the adrenal cortex increases after unilateral adrenalectomy [3]. However, the authors who have studied this problem have made a count of the mitoses throughout the whole cortex, without dividing it into separate zones. Therefore, from their results it is impossible to distinguish the participation of the different cortical zones in the hypertrophy.

TABLE 1. Mean Weight of the Hypertrophied Adrenal at Various Times After the Operation

Time after operation	Series of experiments	No. of animals	No. of animals in which there was hypertrophy	No. of animals in control	Wt. of extirpated adrenal (left)	Wt. of hypertrophied adrenal (right)	Wt. of both adrenals of control animals	Wt. of hypertrophied adrenals as a percentage of control adrenals
					in mg			
24 h	I	11	8	4	14.5	18.6	29.0	64
	II	9	7	—	12.1	16.1	22.6	71
	III	9	7	—	14.7	19.5	22.2	88
2 weeks	I	8	7	5	16.5	26.2	36.0	70
5 weeks	I	9	9	10	11.8	22.9	34.0	67
7 weeks	II	13	11	5	17.7	26.1	36.0	70
$4^1/_2$ months	I	13	13	10	13.2	25.3	37.0	70
	II	20	18	9	16.2	25.9	39.2	66
	III	6	5	4	15.6	28.2	42.0	67

The object of the present work has been to make a more detailed investigation of hypertrophy of one adrenal occurring after removal of the other.

EXPERIMENTAL METHOD

The left adrenal was extirpated from 200 male white rats weighing 120-180 g, in which, as is well known, the right gland has the greater weight [1, 13]. In our experiments the difference in weight between the left and right adrenal was 0.5-1.5 mg. A mock operation was performed in 20 animals.

TABLE 2. Influence of Operative Procedure on the Weight of the Adrenals.

Operation performed	Number of animals	Wt. of adrenals (in mg) 24 h after the operation		Number of animals	Wt. of adrenal (in mg) 7 days after the operation	
		left	right		left	right
Extirpation of left adrenal	9	12.5	16.0	9	13.7	18.6
Mock operation	10	15.8	14.2	10	14.5	13.5
Control (no operation	10	13.5	12.6	10	16.1	15.5

They were killed with ether vapor 24 h, 7 and 10 days, 2, 5, and 6 weeks, and $4^1/_2$ months after the operation, at the same time as the control animals. The adrenal glands of both experimental and control groups were weighed on torsion scales; they were fixed in Carnoy, embedded in paraffin, and serial sections 6 μ thick were cut and stained in hematoxylin-eosin. Every 6th section was drawn on millimetre paper with the use of an Edinger apparatus giving a magnification of 16 ×. The outlines were drawn of the zona glomerulosa, zona fasciculata and reticularis, and of the medulla. The parts corresponding to each zone were cut out separately and weighed on torsion scales. The area of the separate zones was expressed in arbitrary units, the unit being equal to the weight of a square centimetre of millimetre paper. For this purpose the figures for each zone were divided by 7 (7 mg being the weight of one square centimetre of the paper).

TABLE 3. Area of Adrenal Cortex (in arbitrary units) After Unilateral Adrenalectomy

Time after operation	Glomerular zone					Fascicula-Reticular zone					Medulla				
	expt.		control			expt.		control			expt.		control		
	No. of animals	area	No. of animals	area	P	No. of animals	area	No. of animals	area	P	No. of animals	area	No. of animals	area	P
24 h	8	4.7	8	5.0	—	8	43.0	8	33.0	0.012	8	6.1	8	5.3	0.338
7 days	9	7.7	5	6.2	0.253	9	59.0	5	34.4	0.001	9	8.7	5	6.5	0.044
$4^1/_2$ months	6	6.0	5	6.5	—	6	55.2	5	43.4	0.055	6	8.6	5	8.8	—

The mitoses were counted in sections of adrenals fixed 24 h after the operation which was performed on 5 experimental and 5 control animals. The rats were killed between 10 and 11 A. M. i.e., at the time when mitotic activity in the zona fasciculata was at a maximum [5]. The mitoses were counted under a binocular microscope having an immersion objective of 60 × and an ocular of 10 ×: the count was made separately in the glomerular and external fasiculate zones without division into internal fasciculate and reticular zones. We were unable to distinguish the internal fasciculate from the reticular zone, particularly in animals with hypertrophied adrenals. The mitotic index was calculated as numbers per thousand cells, and all the results were treated statistically by the method of Fischer-Student.

EXPERIMENTAL RESULTS

The results for the weight of the adrenals of the experimental and control animals at various times after the operation are given in Table 1 (we considered only cases when the weight of the right adrenal had increased with respect to the original weight of the left adrenal at the time of the operation).

In 2 sets of experiments in which the animals were killed 24 h after the operation, as controls we used the left adrenals removed at operation; we could assume that during this short time the weight of the adrenals of the intact animals had not altered. The results given in Table 1 show that even after 24 h adrenal hypertrophy had occurred. The index of hypertrophy was on average 74% (mean of 3 sets of experiments). The difference between

TABLE 4. Mitotic Activity in the Different Zones of Adrenals of the Experimental and Control Rats

	No. of rat	Glomerular zone			No. of rat	External fasciculate zone			No. of rat	Internal fasciculate and reticular zone		
		no. of cells	no. of mitoses	mitotic index		no. of cells	no. of mitoses	mitotic index		no. of cells	no. of mitoses	mitotic index
Control	1	9,840	6	0.60	1	6,240	1	0.16	1	6,720	0	0.00
	2	7,510	2	0.29	2	6,670	0	0.00	2	7,590	0	0.00
	3	6,960	5	0.70	3	6,100	1	0.16	3	8,970	1	0.11
	4	9,900	4	0.40	4	6,600	2	0.30	4	11,000	1	0.09
	5	8,640	8	0.90	5	5,280	0	0.00	5	11,760	2	0.19
Mean		8,538	5	0.58		6,180	0.8	0.12		9,208	0.8	0.08
Expt.	1	8,328	4	0.40	1	5,520	4	0.70	1	7,440	1	0.10
	2	7,260	4	0.50	2	5,660	1	0.19	2	7,480	0	0.00
	3	7,200	7	0.97	3	5,160	2	0.39	3	7,729	1	0.13
	4	7,420	6	0.80	4	8,250	5	0.5	4	13,000	5	0.39
	5	6,500	2	0.30	5	6,760	1	0.1	5	10,140	1	0.09
Mean		7,341	4.6	0.60		6,270	2.6	0.38		9,158	1.6	0.14

the weight of the right adrenal in the control and experimental groups was statistically significant at a level of P = = 0.007.

Subsequently, the index of hypertrophy varied between 66 and 70%. In some animals the weight of the adrenals reached 80-90% of the weight of the 2 adrenals of the control animals, but never reached 100% of this amount.

As a control the influence of the operative interference on hypertrophy was studied in separate experiments; in the control animals a mock operation was made, i.e., the abdominal cavity was opened, and all manipulations carried out except that no adrenal gland was removed.

From Table 2 it can be seen that 24 h after the operation for removal of the left adrenal the right adrenal in the operated animals weighed more than it did in the controls. The difference was statistically significant (P=0.003). However, there was also a statistically significant difference between the weight of the adrenals of animals who had undergone the mock operation and that of the adrenals in the unoperated animals. The difference between the weight of the left adrenals was statistically significant (P = 0.013), the difference between the weight of the right adrenals was not significantly different (P = 0.106). Seven days after the operation the increase in weight of the adrenals was found only in the experiment in which the left adrenal had been removed (P = 0.001).

Thus, the true compensatory hypertrophy consisting of an increase in the weight of the organ in response to extirpation of the oppostie gland did not develop until 7 days after the operation, i.e., when the influence of stress had ceased. However, an increase in the weight of the adrenal occurring 24 h after the operation is not a compensatory hypertrophy but a response which may be attributed to stress.

Table 3 shows the results of weighing portions of the different zones 24 h, 7 weeks, and $4^1/_2$ months after the operation. A statistical treatment of the results obtained showed that the difference in the size of the glomerular zone in the experimental and control groups was not statistically significant at any of the 3 occasions when the measurements were made. The increase in the size of the fasciculate zone after 24 h and after 7 weeks was significant (P = 0.012 and 0.0001 respectively). After $4^1/_2$ months the difference was nearly significant (P = 0.055). In this case adrenals were found with an increase in size of the fasciculate-reticular zone.

Thus, compensatory hypertrophy of an adrenal occurring after removal of the opposite gland occurs chiefly through hypertrophy of the fasciculate-reticular zone. The glomerular zone is not only not increased, but shows some tendency to reduction. The medulla did not increase until 7 days after the operation, and then only slightly.

Table 4 gives the results of a count of the mitotically dividing cells 24 h after the operation in the glomerular zone, external fasciculate zone, and combined internal fasciculate and reticular zones in 5 experimental and 5 control animals.

In the glomerular zones the mitotic index was the same in both groups. No difference was found either in the distribution of the phases. The dividing cells were situated directly beneath the capsule, or separated from the capsule by 1 or 2 layers of cells.

In the external fasciculate zone we found the dividing cells had increased 3 times ($P = 0.001$). Sometimes the dividing cells were found in clumps. We were unable to find any zone of small cells in which mitoses preponderated [7].

The increase in the size of the fasciculate-reticular zone and the number of dividing cells 24 h after the operation leads us to suppose that the recovery reactions develop in the adrenal early, but they are not fully manifest until 7 days after the operation.

The results we have obtained indicate that in the adrenals, as in other organs, compensatory hypertrophy appears to develop not immediately, but several days after the operation, and leads to the remaining organ increasing to up to 70% of the weight of the 2 glands of the control animals. This weight is maintained for a long time, possibly to the end of life.

SUMMARY

The left adrenal gland was removed from 200 albino rats, and a mock operation was performed on 20 animals. The adrenals were studied 24 h, 7, 10 days, 2, 5, 6 weeks, and $4\frac{1}{2}$ months after the operation.

It was found that 24 h after the operation the weight of the right adrenal gland had increased. There was also an increase in the size of the fasciculate-reticular zone of the cortex, and in the number of mitoses in the external zona fasciculata. However, a gain in the weight of the adrenal gland was found also in the mock operation. Evidently this increase was mainly due to stress.

Seven days after the operation a compensatory hypertrophy could be detected (increase in the size of the organ following excision of the contralateral gland). At these periods no hypertrophy was produced by the mock operation. One, and $4\frac{1}{2}$ months after the operation the weight of the adrenal was 66 to 70% of that of the 2 control adrenals.

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