

REGENERATION OF THE ADRENAL CORTEX UNDER THE INFLUENCE OF ACTH AND PREDNISOLONE

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The experimental studies of regeneration of the adrenal cortex, so far undertaken, have been mainly limited to regenerative processes after unilateral or bilateral enucleation of the adrenal glands [2, 3, 8, 10, 11]. Regeneration in the adrenal cortex after partial adrenalectomy has received very little study. This is particularly true in relation to the effect of ACTH and corticoids on this process, although individual attempts have been made to study repair in this organ during administration of ACTH [2, 3, 8, 9] and of corticosteroid hormones [2, 3].

The object of the present investigation was to study regeneration of the adrenal cortex and the reaction of the residue of the gland after partial adrenalectomy against the background of administration of the hormones ACTH and prednisolone.

EXPERIMENTAL

Experiments were carried out on 67 albino rats weighing 120-160 g, divided into three groups. The animals of group 1 were controls, those of group 2 received ACTH by intramuscular injection in a dose of 4 i.u./100 g body weight/day, while the rats of group 3 received prednisolone by mouth in a dose of 2 mg.

Half the left adrenal and the whole of the right adrenal were resected in all the animals in the course of a one-stage operation under ether anesthesia. The animals were sacrificed 2, 5, 10, 20 and 30 days after the operation. Fragments of the adrenals taken during the operation and after sacrifice were weighed on torsion scales and fixed in Bouin's and Carnoy's solutions and in 10% neutral formalin. Paraffin sections were stained with hematoxylin-eosin, lipids were detected with Sudan IV and Schiff's reagent, and RNA by staining with methyl green-pyronine by Brachet's method. The weights of the adrenals, expressed in mg/100 g body weight of the control animals, were subjected to statistical analysis.

EXPERIMENTAL RESULTS

The adrenal capsule of the control animals in the early periods after the operation (2-5 days) was considerably thickened and looser in structure than in normal animals. Numerous small cells with long or oval, and sometimes irregular, lightly stained nuclei were visible among the fibers of the capsule. As a rule, these cells lay in groups, and less commonly one by one. These cells gradually migrated toward the zona glomerulosa, in which process they acquired the typical characteristics of cortical cells: their nuclei became round, tiny droplets of lipids appeared in the cytoplasm, and the cells increased in size. These cells subsequently became part of the zona glomerulosa or formed bands invading the young connective tissue in the region of injury. Five days after partial adrenalectomy, cells in various stages of transition from undifferentiated capsule cells to the glandular cells of the zona glomerulosa could be seen in the capsule and the zona glomerulosa and the outer zona fasciculata. The cells of the zona fasciculata and zona reticularis at this period were extremely poor in lipids. The cytoplasm of the cells in the capsule, the subcapsular layer, and the zona glomerulosa contained much more RNA than normally.

After 20-30 days, a small protrusion of the newly formed areas of the zona glomerulosa was observed into the region of injury. The defect was covered by regenerating capsule, consisting of bundles of collagen fibers running parallel to the amputation surface, and of cells resembling fibroblasts. The number of sudanophilic droplets in the cells of the zona glomerulosa and zona fasciculata showed an increase at this time.

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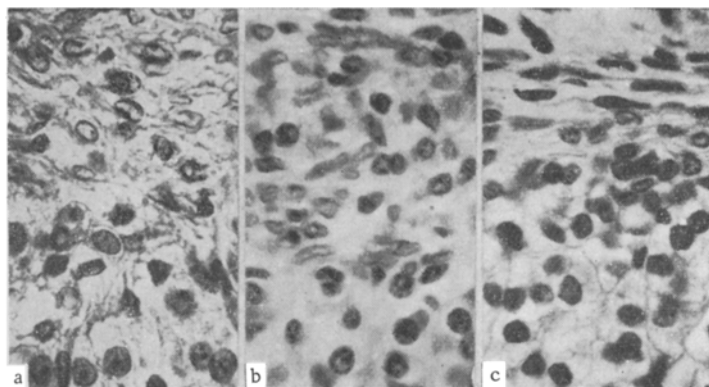


Fig. 1. Undifferentiated cells in the capsule and subcapsular layer of the adrenals. Five days after operation. a) Control; b) after administration of ACTH; c) after administration of prednisolone. Hematoxylin-eosin. Objective 90, ocular 7.

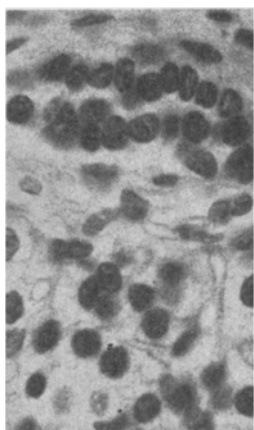


Fig. 2. Formation of a band of cortical cells in the adrenal capsule after administration of ACTH. 10 days after operation. Hematoxylin-eosin. Objective 90, ocular 7.

In the adrenals of the animals receiving ACTH, between 2 and 5 days after the operation the greatly thickened, loose capsule contained many modified cells showing considerable polymorphism (Fig. 1b). Here and there in the capsule islands or bands of glandular cells were formed, separated from the surrounding connective tissue by a basement membrane (Fig. 2). Many mitoses were seen in the capsule, the subcapsular layer, and the zona glomerulosa and the outer zona fasciculata. The cell cytoplasm in the zona fasciculata and zona reticularis was filled with tiny lipid droplets. In the zona glomerulosa the lipid content was somewhat smaller than in the controls. The RNA content in the cells of the capsule, the subcapsular layer, and the zona glomerulosa and zona fasciculata was much higher than in the controls.

In the later stages after the operation (20-30 days) many large foci of cortical glandular tissue could be seen in the adrenal capsule. The defect in the organ was covered by a newly formed, thin connective-tissue capsule. The cortical layer in the remnant of the band was greatly hypotrophied on account of an increase in the thickness of the zona fasciculata. The weight of the remnant of the adrenal was much greater than in the controls (see table).

In the animals receiving prednisolone, in the early stages after the operation the areas of the capsule immediately next to the site of injury were only slightly thickened. In the capsule and subcapsular layer there were a few cells of transitional character, mainly in the early stages of differentiation (Fig. 1c). Isolated mitoses were seen in the zona glomerulosa and the outer zona fasciculata. A high lipid content, in the form of large droplets, was found in the cells of the zona fasciculata. The RNA content in the cells of the capsule, subcapsular layer, and outer zona fasciculata was considerably lower than in the controls. Later, 20-30 days after partial adrenalectomy, no signs of proliferation could be seen in the adrenal cortex. The dense, thin capsule of the gland contained few cells. In the region of injury a dense collagen scar containing mature fibroblasts had formed. The cortical layer was thinner than in the controls because of atrophy of the zona fasciculata. The weight of the remnant of the adrenal was only slightly increased (see table).

Besides hypertrophy in the residual part of the adrenal after partial adrenalectomy, the formation of new tissue was thus observed. This process consisted, first, of the formation of new areas of the zona glomerulosa in the region of injury and, second, of the transformation of undifferentiated cells of the capsule and subcapsular layer into cells of the glandular epithelium of the cortex, leading to the formation of foci of cortical tissue in the adrenal capsule in the animals receiving ACTH. The cells of the capsule and subcapsular layer from which the glandular cells of the cortical epithelium developed must evidently be

Changes in Weight of the Adrenal Remnant after Partial Adrenalectomy under the Influence of ACTH and Prednisolone (in mg/100 g body weight of control animals)

Experimental conditions	No. of observations	Remnant	Days after operation					P	Increase in wt. of tissue (as percent of remnant)
			remnant and regeneration						
			2	5	10	20	30		
Partial adrenalectomy (control)	7	6,7±0,76	14,3±1,04	12,1±0,95	11,1±1,78			<0,01	113,3
	11	7,5±0,85						<0,001	61,3
	8	5,5±0,87					12,0±1,60	<0,01	102,0
	8	7,2±0,10						<0,01	54,2
	8	6,7±0,93						<0,05	79,1
Partial adrenalectomy + ACTH	4	10,1±1,87	11,0±0,84	19,3±1,84	16,6±1,77			>0,05	8,9
	11	12,1±1,30						<0,05	60,8
	11	7,3±1,38				15,8±1,22	24,0±2,80	<0,01	147,7
	6	10,1±1,02						<0,05	56,5
	5	8,5±1,93						<0,001	182,4
Partial adrenalectomy + prednisolone	4	5,4±1,40	8,4±1,26	8,1±1,10	6,7±1,11			<0,05	55,5
	12	4,7±0,81						<0,01	72,4
	14	6,3±1,14				4,2±0,90	7,4±1,88	>0,05	6,3
	6	3,6±0,92						>0,05	16,7
	5	6,5±1,04						>0,05	13,8

regarded as specific "cambial" cells of mesodermal origin, similar to those from which the adrenal cortex is formed in ontogenesis [5]. In this respect our results concur with the observations of several other investigators [2-4, 6-8, 10, 11].

The effect of ACTH on regeneration in the adrenal cortex was to some extent opposite to the action of prednisolone on this process, a phenomenon which is not observed in other organs and tissues [1]. It is dependent on the specific action of these hormones on the adrenal cortex and associated with variations in the intensity of function of the gland.

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