COMPARATIVE CHARACTERISTICS OF COMPENSATORY ADRENAL HYPERTROPHY IN MATURE AND OLD RATS

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KEY WORKS: unilateral adrenalectomy; compensatory hypertrophy; index of hypertrophy; maturity and old age.

The compensatory powers of the adrenal gland in old age, exhibited in the case of loss of the contralateral organ, have virtually not been studied [5]. There is evidence that the level of compensatory capacity of the adrenal gland of mature rats changes only a little with age [8]. It has been suggested, on good grounds, that in old animals a new level of corticosteroid synthesis is established, able to restore a state of optimal homeostasis after various events [4].

The object of this investigation was to compare the response of the adrenal glands to unilateral adrenalectomy in old animals and in animals of reproductive age.

EXPERIMENTAL METHOD

Noninbred male albino rats aged 25 months (experiments of series I) underwent unilateral adrenalectomy and were sacrificed 1, 3, 5, 7, 14, 21, and 30 days after the operation. At the time of operation, rats identical in age and weight acted as the control and were killed at the same times. Six experimental and four or five control rats were used at each time of the investigation. The body weight of the animals was determined immediately before the operation and after sacrifice, and the weight of the removed and hypertrophied adrenal glands of the experimental rats was measured. The body weight of the control rats initially and before sacrifice and the weight of the left and right adrenals were determined. Two indices of hypertrophy (IH) were calculated [3]. The first (IH-1) was calculated as the ratio of the weight of the hypertrophied right adrenal to the weight of the right adrenal in the control, the second (IH-2) was calculated as the ratio of the weight of the hypertrophied adrenal to the combined weight of both control adrenals. The adrenals were fixed in Carnoy's fluid and subjected to histological treatment. Paraffin sections 5 μ thick, taken from the middle part of the gland, were stained with hematoxylin and eosin. By means of an ocular micrometer the width of the zona glomerulosa and zona fasciculata + zona reticularis of the adrenal cortex was measured in the section with maximal area of medulla (the structural middle of the organ) at four opposite points in accordance with the writers' own scheme (Fig. 1). The arithmetic mean width of each zone, for the hypertrophied adrenal and both control adrenals, was calculated. The results were subjected to statistical analysis by the Fisher—Student method. For comparison, mature rats aged 3 months were investigated in exactly the same way (experiments of series II). At each time of the investigation there were 8-10 experimental and 8-10 control animals.

EXPERIMENTAL RESULTS

The experiments showed that the operation and the disturbances of hormonal balance arising as a result of it did not affect the body weight of the old animals for almost 3 weeks. Not until after 21 days was the weight of the experimental rats found to be a little below that of the control. The body weight of the mature experimental rats exceeded that of the control on the 21st day ($P < 0.01$), but later it also began to fall behind ($P < 0.001$).

The residual adrenal gland in all the old rats (irrespective of the time after operation) underwent hypertrophy and attained a very large size. However, the process of development of

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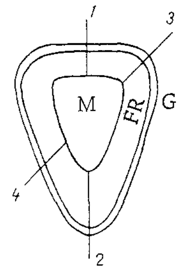

Fig. 1

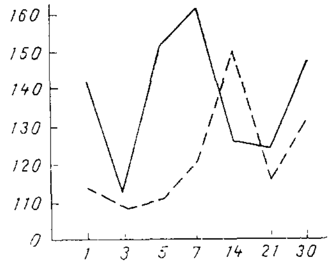

Fig. 2

Fig. 1. Diagram of structure of rat adrenal gland and vectors used to measure width of cortical zones. G) Zona glomerulosa; FR) zona fasciculata + zona reticularis; M) medulla; 1-4) vectors of measurement.

Fig. 2. Degree of compensatory hypertrophy of right adrenal after left-sided adrenalectomy (in % of control) in old and mature (broken line) rats. Abscissa, time after operation (in days); ordinate, IH (in %).

hypertrophy followed a fluctuating course. On the first day after the operation the increase in weight of the residual right adrenal was 142.0% relative to the weight of the control right adrenal (IH-1). Such a marked increase in weight during the first day could be due to a stress reaction of the organ in response to the operation. By the third day the increase was smaller, but later it increased rapidly, to reach a maximum (163.0% of the control) by the 7th day. During the next 2 weeks the increase in weight of the gland was reduced, but toward the end of the first month after the operation it again showed a marked increase. To discover how far the deficit in weight of the gland had been made good, the weight of the hypertrophied adrenal was compared with the combined weight of the two control adrenals. The value of IH-2 was found to be very high at these times of the investigation (Table 1). However, at no time was a value of IH-2 of 100% recorded, i.e., the weight of the residual gland did not increase to equal the combined weight of both control glands. The maximal increase in IH-2 occurred on the 7th day after the operation and amounted to 74.5%.

Analysis of the change in weight of the residual adrenal in mature rats showed that the process of increase in weight also followed a fluctuating course. The dynamics of the fluctuations was similar in its basic features to that observed in old rats, namely: On the 1st day after the operation the organ increased in size a little (as the response to stress), on the 3rd day the increase in its weight was less than in the control, and by the 14th day there was a marked increase, to be followed by another decrease on the 21st day; toward the end of 1 month after the operation a further increase was observed.

Comparison of the results of weighing the adrenals of the old and mature rats showed that at nearly all times of the investigation adrenal hypertrophy was much greater in the old rats than in the mature animals. Comparison of these same data represented in graphic form (Fig. 2) suggested that not only was the degree of compensatory hypertrophy of the adrenals in the old rats greater than that in rats of mature age at these times of investigation, but the actual process itself began to develop much sooner. Furthermore, in the old rats the increase in weight of the gland took place faster than in mature rats, and the decline in the increase in weight relative to the control took place more slowly (Fig. 2).

Reactive changes in the adrenal cortex of the old and mature rats developed similarly. The zona glomerulosa of the experimental old rats was wider than in the control during 5 days after the operation ($P < 0.05$), after which it narrowed sharply ($P < 0.05$). Later the width of the zona glomerulosa increased a little ($P < 0.05$), but no longer reached the control level. The zona glomerulosa, incidentally, had its minimal width at a time of maximal increase in size of the gland (7th day), and subsequent widening coincided in time with a decrease in the degree of growth of the gland (14th day).

In the experimental mature rats the width of the zona glomerulosa was less than the control at all times of the investigation ($P < 0.05$). On the whole the changes taking place in this parameter in the experimental mature rats throughout the period of investigation were comparatively small, by contrast with the marked, step-like changes observed in series I.

TABLE 1. Body Weight, IB, and Width of Zones of Adrenal Cortex in Mature (II) and Old (I) Rats after Unilateral Adrenalectomy

Series of experiments	Time after operation, days	Increase in body weight of experimental rats, % of initial	Increase in body weight of control rats, % of initial	IH-1	IH-2	Width of zona glomerulosa, % of control	Width of zona fasciculata + zone reticularis, % of control
I	1	98,31	100,25	142,03	66,38	108,94	97,71
II		105,63	105,27	114,09	53,97	89,19	107,53
I	3	100,80	100,25	113,08	52,82	104,47	102,11
II		110,63	113,22	109,20	52,90	97,84	93,62
I	5	100,33	100,00	152,26	73,90	124,92	122,79
II		115,00	108,05	111,25	54,45	89,52	110,91
I	7	99,04	103,02	162,97	74,46	68,95	137,08
II		116,83	112,58	121,36	60,40	85,43	101,90
I	14	101,27	100,22	125,70	57,92	98,67	112,43
II		114,58	107,93	149,84	69,84	82,01	119,10
I	21	102,18	105,41	124,52	57,98	86,96	116,12
II		114,36	132,38	115,58	55,36	89,38	106,25
I	30	107,50	115,79	146,88	69,21	88,95	107,09
II		120,32	121,39	131,64	64,11	83,36	115,17

The combined zona fasciculata + zona reticularis of the old adrenalectomized rats reached values above the control level starting with the 3rd day after the operation, and it increased to a maximum on the 7th day. At subsequent times the degree of hypertrophy of this zone decreased, but under these circumstances there was a tendency for it to exceed the control level.

In mature rats the width of the combined zona fasciculata + zona reticularis changed in a stepwise fashion compared with the control. On the 1st day after the operation the zone widened, to exceed its width in the control, on account of postoperative stress and congestion of the blood vessels, but this was followed by narrowing. Starting with the 3rd day hypertrophy of the zona fasciculata + zona reticularis proceeded unevenly. The considerable increase in size of the zone in adrenalectomized mature rats reached a maximum on the 14th day, which corresponded to the time of maximal increase in weight of the residual gland (Table 1), It is a particularly interesting fact that in most cases widening of the zona fasciculata + zona reticularis was much less in degree in mature rats than in the old animals.

Rats aged 25 months, i.e., for practical purposes old rats, thus showed no inhibitory effect on the realization of the compensatory powers of their adrenal gland. Moreover, the degree of hypertrophy of the gland in the old rats was observed to be a little greater than in mature animals. This enhanced response of one component of the hypothalamic-hypophyseal-adrenocortical system to a sudden fall in the corticosteroid level in old age is due to the necessity of maintaining homeostasis against the background of age extinction of other systems maintaining the organism in a stable state. The results do not fully agree with the fairly widely held view that with age the ability to adapt to changing conditions is impaired [7]. At the same time, the available results of a comparative morphological and physiological investigation of the human adrenals between ages of 30 and 82 years [2] are evidence, on the contrary, of the high secretory potential of this organ throughout life. The results of the present experiments suggest that the mineralcorticoid-producing system is very stable in old age. Verzar [8] notes that in advanced old age a definite increase in the ability of the adrenal glands to exhibit adaptive growth can be observed. This phenomenon has been found also in the case of the kidneys, during a study of their ability to undergo compensatory growth at different ages [6]. Finally, in the regulatory concept of the neuroendocrine mechanism of development and aging, a compensatory intensification of the functions of certain endocrine glands with age is seen to be a characteristic phenomenon [1]. The results of the present experiments in turn confirm the fact of activation of certain compensatory-adaptive mechanisms in old age. The histophysiological basis of this phenomenon requires further elucidation.

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PREVENTION OF STRESS AND ANOXIC HEART DAMAGE BY THE GLUCOCORTICOID DEXAMETHASONE

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Severe emotional-painful stress (EPS) is known to cause damage to the cells of the myocardium and to disturb its contractile function [1]. The principal pathogenetic element of this stress injury is an increase, many times over, in the blood catecholamine concentration [9] and, in turn, this leads to the development of the lipid triad and to injury to the cell membranes [2]. However, the fact is worth noting that administration of exogenous catecholamines and their synthetic analogs to animals in doses comparable with those observed during stress causes more severe damage to the myocardium than stress itself, although in a stress situation a high catecholamine level is maintained for a long time [3, 11]. In other words, one of the many factors of stress has a stronger damaging action on the heart than the stress reaction as a whole.

These observations suggest that in stress besides the harmful action of an excess of catecholamines, a cardioprotective effect of other hormones also is exhibited. This action may be exerted above all by glucocorticoids which, according to some data, are stabilizers of biomembranes [10, 12], they reduce the degree of ischemic damage to the myocardium [5, 12], and restrict loss of enzymes accompanying such damage [5].

The object of this investigation was to study the possibility of protection of the heart against stress damage by preliminary administration of the glucocorticoid dexamethasone (DM).

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 220-250 g. The animals were divided into four groups: 1) control rats, 2) rats receiving DM in a dose of 5 mg/kg intraperitoneally 7 h before sacrifice, 3) rats exposed to EPS by the method in [6] for 6 h, and 4) rats receiving DM before stress in the same dose as the animals of group 2.

The heart was removed under urethane anesthesia 1 h after the end of EPS and was perfused with Krebs–Henseleit solution, oxygenated with a gas mixture containing 95% O_2 and 5% CO_2, at 37°C. The contractile function of the left ventricular myocardium was investigated under isovolemic conditions by the method in [7]. In the course of the experiments a definite heart rate was imposed by means of an ESL-1 apparatus. The coronary blood flow was determined at a frequency of 120 beats/min. After perfusion of the heart for 90 min under conditions of normal oxygenation — with minimal release of creatine phosphokinase (CPK) into the perfusion fluid, anoxia was created. The perfusion solution was then aerated with a mixture containing 95% N_2 and 5% CO_2. This anoxic procedure lasted 10 min, and was followed by reoxygenation also for 10 min.

CPK activity was determined in the perfusate which had passed through the coronary system by the method in [4] at the 90th minute of perfusion during normal oxygenation, at the 10th minute of anoxia, and at the 2nd minute of reoxygenation.

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