MECHANISM OF THE EFFECT OF IONIZING RADIATION ON SUPRARENAL FUNCTION

Part I. Role of the Hypophysis in Regulating the Suprarenal Cortex Following Small Internal Doses of Radiation

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According to the description of the general adaptation syndrome [7], the hypophysis is the sole regulator of adrenal cortical function, the anterior lobe secreting adrenocorticotropic hormone (ACTH). Until now, attempts to reveal other mechanisms controlling cortical function have failed [2, 3]. Nevertheless, there are reports that changes in the adrenal cortex, and particularly those occurring in radiation sickness, cannot be attributed to changes in the secretion of ACTH [4]. It has been shown [1, 4] that functional changes in the adrenal cortex are not the direct result of the action of radiation on tissue, but are brought about indirectly.

The present article reports work in which an attempt was made to determine the extent to which the hypophysis was involved in adrenal cortical damage caused by small doses of radiation.

METHOD

The experiments were carried out on intact and on hypophysectomized male rats not less than ten days after the operation. 50 μC of Na^{24} were given to each rat weighing 250 g. We first established that the dose produced by the breakdown of this quantity of isotope is always effective, but exceeds only by one order the dose which produces no statistically significant changes in adrenal cortical function in intact rats. Adrenal cortical secretion was determined from changes in the weight of the thyroid gland (as indicating the condition of the thymus and lymphatic system), weight of the adrenal glands, and their content of ascorbic acid (as determined by Tilman's titration method). On each occasion 20 animals were used. The results were treated statistically.

RESULTS

A solution of radioactive sodium carbonate $Na_2^{24}CO_3$ having an activity of 50μC given by mouth caused marked changes in the adrenal cortical functional indices (Fig. 1).

For the first few days, when the total dose of internal β - and γ -radiation amounted to 1.75 REP, the adrenal ascorbic acid had fallen from the control value of 413 to 360 mg%; both here and later, average figures are given. The maximal reduction in ascorbic acid (down to 290 mg%) was recorded on the third day after beginning the irradiation, when the absorbed dose was approximately 7 REP, i.e., at about the time when the injected radioactive sodium-24 had broken down completely.

An increase in adrenal weight occurred during the first few hours after irradiation. The greatest effect was produced by an internal dose of 6.7 REP, when the adre-

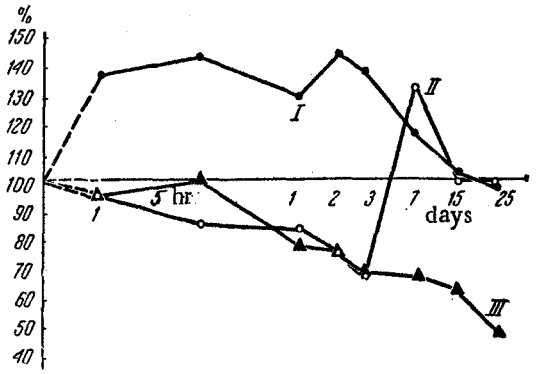

Fig. 1. Functional adrenal cortical changes following administration of 50 μC Na^{24}. Abscissa – time of observation on logarithmic scale; ordinate – percentage difference of the experimental and control indices. I) Change in weight of adrenals; II) change in adrenal ascorbic acid content; III) change in weight of thymus.

nals attained a weight of 228 μg/g per kg (as compared with the control value of 156 μg /g).

After 24 hours irradiation, the weight of the thyroid was 2.5 mg/g, which was less than the control value of 3.2 mg/g. The thymus continued to diminish in size during the whole observation period, and in some animals it disappeared altogether. Twenty five hours after giving the isotope, the weight of the thyroid had fallen to 1.5 mg/g.* These results show that, at any rate, for the first three days the signs of adrenocortical hyperfunction are typical of those produced by stress.

After one week, the weight of the adrenals returned to normal, but the ascorbic acid content was increased, and did not return to normal until the 15th day.

Having ascertained that the greatest biochemical changes in the adrenals occurred on the third and seventh day after irradiation, we arranged a similar set of experiments on 60 hypophysectomized animals of which 20 were controls, and 20 were tested on the third and seventh day after receiving 50 μC of radioactive Na^{24}.

The results were as follows. Hypophysectomy itself causes a reduction in weight of the adrenals. In the control intact animals, the relative weight of the adrenals was 156 μg/g, and in the control hypophysectomized group it was only 40 μg/g. The marked atrophy of up to 75% of the adrenal tissue following hypophysectomy has been described many times previously. It is, however, interesting that other indices of adrenocortical function (weight of thyroid and ascorbic acid content of adrenals) differed very little from their values in the control intact animals.

In general, giving radioactive Na^{24} to hypophysectomized rats produced the same reactions of the adrenal cortex as it did in the intact animals.

On the third day there was a small but statistically significant increase in adrenal weight up to 47 μg/g, a reduction in their ascorbic acid content from 391 to 337 mg%, and a reduction in weight of the thyroid from 3.2 to 2.7 mg/g. However, the difference from the mean was only half that of the unoperated experimental group at the corresponding period. It is quite likely that the reason why certain authors [5, 6], who worked with a smaller number of animals, have denied the existence of these changes is because they are so small, and it is only through the statistical treatment of our results that the validity of the changes has been established.

Apparently the time which elapses between hypophysectomy and irradiation is important. It appears that the aftereffects of the strong stress caused by the operation and trepanning of the base of the skull continue to operate for about one week. Seven days after the isotope had been given (Fig. 2b), the weight of the adrenals in the hypophysectomized animal returned to normal, the ascorbic acid was somewhat increased (453 mg%), and the weight of the thyroid was further reduced (down to 2.5 mg/g), i.e., the same changes which were observed in the intact animals occurred. Here again, although it was statistically significant, the extent of the change was far less than it was in the intact animals.

The results presented here show that the hypophysis exerts a stimulating effect on the adrenal cortex. It is also evident that this is not the only possible means

*Further evidence for the reduction in the lymphoid tissue following equivalent doses of internal radiation has been produced by other workers in our laboratory, who studied the blood cells and the hemopoietic organs.

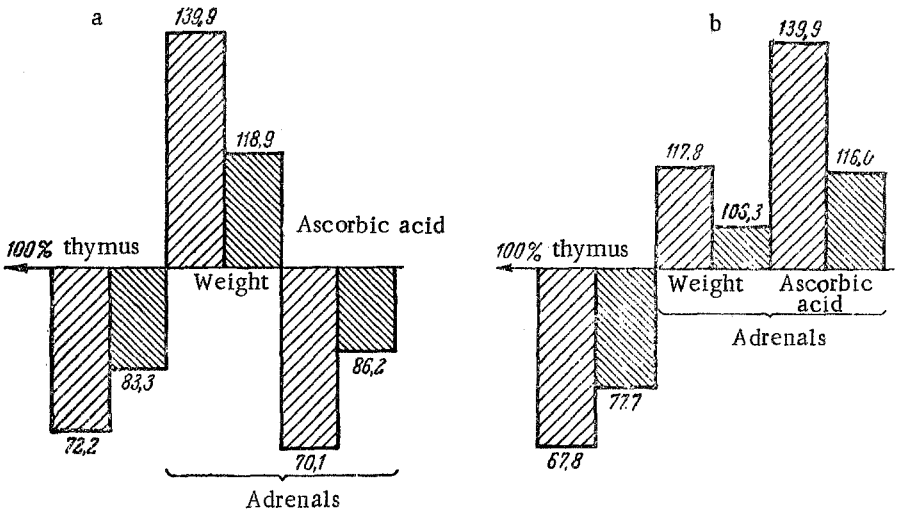

Fig. 2. Variation of the adrenocortical functional indices in hypophysectomized and intact rats as a percentage of the control values (taken as 100): a) on the 3rd day and b) on the 7th day after receiving 50 μC of Na^{24}. The columns with the widely spaced shading represent the indices of the intact animals; those with the closer shading refer to the hypophysectomized animals.

whereby the adrenal cortex may be stimulated, at any rate, as far as the effects of radiation are concerned.

While it is possible that radiation exerts a direct effect on the adrenals, it is probable that another mechanism or mechanisms exist whereby the adrenals are brought to respond to small doses of radiation administered internally.

SUMMARY

The reaction of the adrenal cortex, as judged by weight changes, changes in the amount of ascorbic acid, and in the weight of the thymus in intact and hypophysectomized rats was measured after administration of 50 μC of Na^{24}. An amount of radiation equal to 7 REP given internally caused an increase in adrenocortical function in the intact animals. Hypophysectomy, performed ten days before irradiating, reduces, but does not eliminate, these changes. This result suggests that some parahypophyseal influence on the adrenal cortex is involved in the reaction to internal radiation.

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