HYPERTROPHY OF THE ADRENAL CORTEX

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Hypertrophy of the adrenal cortex has not been adequately studied. There is no unanimity in the literature about its nature, and some writers describe as hyperplasia states in which the number of cells is not increased, or no increase has been proved [4, 9]. Descriptions of hypertrophy in most cases are qualitative in character, and not all investigators have described a change in the width of the individual cortical zones and in their weight [1, 3, 5, 8].

In essential hypertension (EH) and, in particular, in its "benign" form, the weight of the adrenals and the volume of the nuclei and nucleoli of the zona glomerulosa and zona fasciculata–zona reticularis (ZG and ZFR, respectively) of the cortex are increased [10]. To continue the study of the principles of development of adrenocortical hypertrophy, the human and rat adrenals were investigated during long-term functional loading associated with disturbances of regulation of the blood pressure and water and salt metabolism.

EXPERIMENTAL METHOD

The adrenals of ten rats of the Okamoto Aoki Strain with genetically determined spontaneous hypertension (SHR), of 20 patients with "benign" EH (BEH) dying from cerebral hemorrhage or myocardial infarction, of 9 patients with "malignant" EH (MEH), dying from renal failure, and of 12 children with the salt-losing form of the adrenogenital syndrome (SLF AGS), dying with similar manifestations of water–electrolyte disturbances between the ages of 1 and 6 months were investigated (in SLF AGS the inborn 21-hydroxylase block leads to aldosterone and cortisol deficiency, which is accompanied by a salt-losing syndrome and a high plasma ACTH level). Adrenals of 10 Wistar rats and 10 noninbred rats, of 15 healthy persons dying from accidental causes with a minimal terminal period, and of 7 babies dying from mechanical asphyxia constituted the control groups. The adrenals were weighed. In paraffin sections 5 μ thick, stained with hematoxylin and eosin, the area of ZG and ZFR of the adrenal cortex was measured with occular grid, and also by tracing the outlines of the zones by means of a drawing apparatus on squared paper. Nuclei and nucleoli were traced in the same way under a magnification of the microscope of 1350, and their volumes were calculated by the equations for a sphere and an ellipse (for 50 nuclei with nucleoli in each zone of the cortex of the human adrenal and 30 nuclei in the case of rats).

EXPERIMENTAL RESULTS

In SHR rats an increase in weight of the adrenals and in the volumes of the nuclei (V_n) of the ZG cells and of the nucleoli (V_{no}) of both zones was found. The nucleo-nucleolar ratio (NNR) was significantly reduced in the zona fasciculata (ZF) (34.93 and 21.66; $P < 0.001$).

In both forms of EH the weight of the adrenals was increased but the ratio between the areas of ZG and ZF was unchanged, i.e., their hypertrophy was comparatively uniform. No signs of hyperplasia could be found. The volumes of the nuclei and nucleoli in both zones of the cortex were increased in BEH by about twice, and almost to an equal degree, so that the values of NNR differed only a little from the control. In MEH the nuclei in both zones of the cortex were enlarged about 3 times, and the nucleoli 5 times, so that NNR was lower than in the control and in BEH ($P < 0.01$ and < 0.05, respectively).

Correlation analysis revealed moderately strong or weak correlations in the control groups of rats between V_n and V_{no} in both zones of the cortex, and in SHR rats strong correlations were found between V_n and

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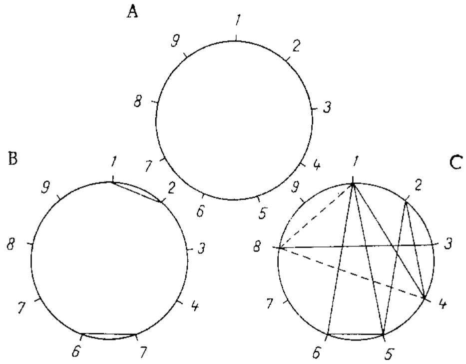

Fig. 1. Correlations between parameters of adrenal cortex. A) control; B) BEH; C) MEH. 1) V_n of ZG; 2) V_{no} of ZG; 3) NNR in ZG; 4) area of ZG; 5) V_n of ZF; 6) V_{no} of ZF; 7) NNR in ZF; 8) area of ZF; 9) weight of adrenals.

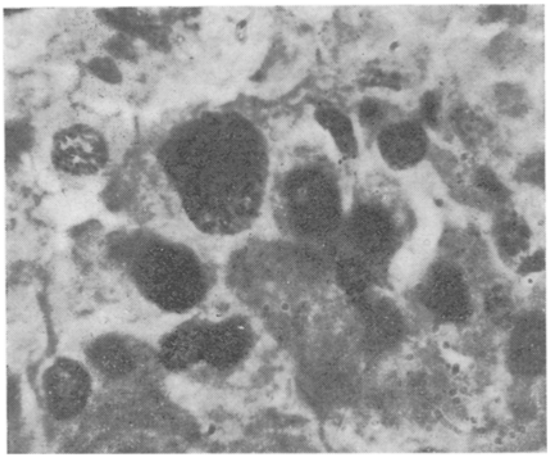

Fig. 2. Mitosis in cell in ZF of adrenal of a premature infant (hematoxylin and eosin; 1200 ×).

V_{no} in ZF ($r = +0.82$). Correlations between parameters of the adrenal cortex in autopsy material in the control series were weak or absent. In BEH moderately strong positive correlations appeared between V_n and V_{no} in both zones ($r = +0.63$ in ZG and $r = +0.66$ in ZF), whereas in MEH strong positive or negative correlations were observed between almost all the parameters of the adrenal cortex studied, i.e., not only within the zones, but also between them (Fig. 1).

In SLF AGS the weight of the adrenals was increased by 2-6 times. As a rule ZG was present in the form of separate islets, and the bulk of the adrenal cortex consisted of ZF. A few cells of the fetal cortex were diffusely scattered throughout the area of the definitive cortex. Hypertrophy of the nuclei was observed in both zones, but it was more marked in ZF and was combined with nuclear polymorphism and hyperchromatism. In two cases mitoses were found in cells of ZF in an infant 17 days after birth at term, and in a premature infant aged 1 month (Fig. 2). Besides the nuclei, the nucleoli also were enlarged (increased in volume and number); in ZF, moreover, the number of nucleoli counted per cell was significantly greater than in ZG. The quantity of "nucleolar material" (the sum of the volumes of the nucleoli in the cell) was increased in ZG mainly on account of an increase in their volumes, but in ZF on account of an increase in their number. Changes in the cell nuclei of ZG thus pointed to hypertrophy, whereas in ZF both hypertrophy and hyperplasia were observed. The increase in the quantity of "nucleolar material" in both zones exceeded the increase in the volumes of the nuclei.

During long-term functional loading some general principles of hypertrophy of the adrenocortical cells were thus discovered. They were basically similar to those discovered previously for regenerative hypertrophy as a whole, allowing for age differences [6, 7]. In SHR rats and in the various forms of EH the hypertrophy is the principal factor, and in man, possibly, the only factor determining the increase in weight of the cortex. Hyperplasia of the cells, however, was found during the period of growth and formation of the definitive cortex, when the plasma ACTH level was high in SLF AGS. Hyperplasia of the cells in ZF evidently is accompanied by hyperplasia of the intracellular structures, as was shown in particular by a proportional increase in the number of nucleoli. In ZG, where hyperplasia was not present, only the volume of the nucleoli was increased.

These differences in the degree of hypertrophy of the nuclei and nucleoli may be attributed to differences in the intensity of adrenocortical function in different pathological states [2]. In BEH, for instance, hypertrophy of the nuclei and nucleoli in ZG and ZF was proportional, but in MEH and SLF AGS the increase in the volumes of the nucleoli was greater and it preceded the increase in volumes of the nuclei. Similar changes also were observed in ZF of the adrenals in SHR rats. The increased functional load on the adrenocortical cells and, in particular, the secondary hyperaldosteronism in MEH and in 15-20% of cases of BEH [11-13] are reflected, on the one hand, in their hypertrophy and, on the other hand, in the stronger correlations between the morphological parameters of these cells (stronger correlations between elements of the system correspond to an increase in the functional load on it).

It can thus be concluded from this investigation that hypertrophy of the adrenocortical cells during functional loading is the principal cause of the increase in weight of the cortex. At an early age the weight of the cortex can also increase in another way, by an increase in the number of cells.

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