

THE INFLUENCE OF THE MITOTIC REGULATORS ON THE NUCLEIC ACID CONTENT OF THE CELL

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The processes of cell division in the animal body are under the control of a neurohumoral regulatory system. In this regulation an important part belongs to the hormone of the adrenal gland. Adrenalin is a powerful inhibitor of cell division and has a wide range of activity [1-5, 11]. The adrenal cortical hormone — cortisone — also possesses antimitotic activity, but its influence on cell division is more selective. Cortisone reduces the mitotic activity in the lymphoid tissues and, to a lesser degree, in the ectodermal epithelium. It has no action on the division of the epithelial cells of the intestine [1, 3]. The mode of action of the mitotic regulators on cell division is not yet clear. It has been shown by several histochemical [9, 10 and others]* and experimental [6, 7] investigations that one of the fundamental biochemical processes with which cell division is connected is the metabolism of the nucleoproteins. These findings suggest that the influence of the mitotic regulators on cell division, and in particular that of adrenalin and cortisone, is effected through the nuclear metabolism of the cell.

In this connection we undertook experiments in which histochemical methods were used to study the nucleic acid content of cells during inhibition of mitosis by adrenalin and cortisone.

EXPERIMENTAL METHOD

Experiments were carried out on white mice of the same litter, 2 months old. Investigations were made of the epithelium of the cornea, skin, tongue and intestine and of the lymphocytes of the thymus gland and the lymphatic glands. In addition to these cells, which possess high mitotic activity, studies were made also of the liver cells, which in adult animals lose their power of mitotic division. These cells were selected mainly on account of their accessibility for histochemical investigation. The material was fixed in Gall's mixture. Ribonucleic acid (RNA) was revealed by pyronine and methyl green by Brachet's method, and desoxyribonucleic acid (DNA) by the Feulgen reaction.

In the first series of experiments the nucleic acid content was studied after injection of the animals subcutaneously with adrenalin in doses of 0.05, 0.5 and 1 mg/kg body weight of the animal. Injection of the drug was repeated twice at intervals of 1½ hours. The animals were killed 1 hour 30 minutes, 3 hours and 4 hours after the last injection. Selection of the dosage of the drug and the time of examination of the material was dictated by findings obtained in the laboratory on the changes in mitotic activity during similar experiments. As a control to this series of experiments white mice were used, kept under identical conditions but not receiving adrenalin.

In a second series of experiments white mice were injected subcutaneously or intraperitoneally with cortisone in a dose of 2.5 mg/kg body weight. In the first group of these experiments cortisone was injected once, in the second group — twice in the course of 24 hours, and in the third group 5 injections of cortisone were given in the course of 72 hours. In all the groups of experiments the material was examined 4 hours after the last injection. For a control animals were used which were kept under identical conditions and received injections of corresponding doses of physiological saline. The number of injections and the time of killing of the animals were determined from consideration of the findings on changes in mitotic activity in similar experiments.

* As in original

EXPERIMENTAL RESULTS

The results of the first series of experiments showed that the injection of adrenalin not only caused a fall in the mitotic activity but considerably altered the nucleic acid content of the cell. Injection of adrenalin in a dose of 0.05 mg/kg body weight causes a marked fall in the DNA and RNA contents of the corneal epithelium and the liver cells. In the epithelium of the skin, the tongue and the intestine no changes in the nucleic acid content were observed. Analogous results were given by the injection of adrenalin in a dose of 0.5 mg/kg body weight. The clearest results were obtained after injection of adrenalin in a dose of 1 mg/kg body weight. In this case an obvious fall in the RNA and DNA contents was observed in the epithelium of the cornea, the skin and the tongue and in the liver cells (Fig. 1). In the intestinal epithelium and the lymphocytes of the thymus and lymphatic glands, no fall in the RNA and DNA content was observed even after a second injection of adrenalin. Only in isolated experiments in which small quantities of adrenalin were injected was there a slight fall in the nucleic acid content of the lymphocytes.

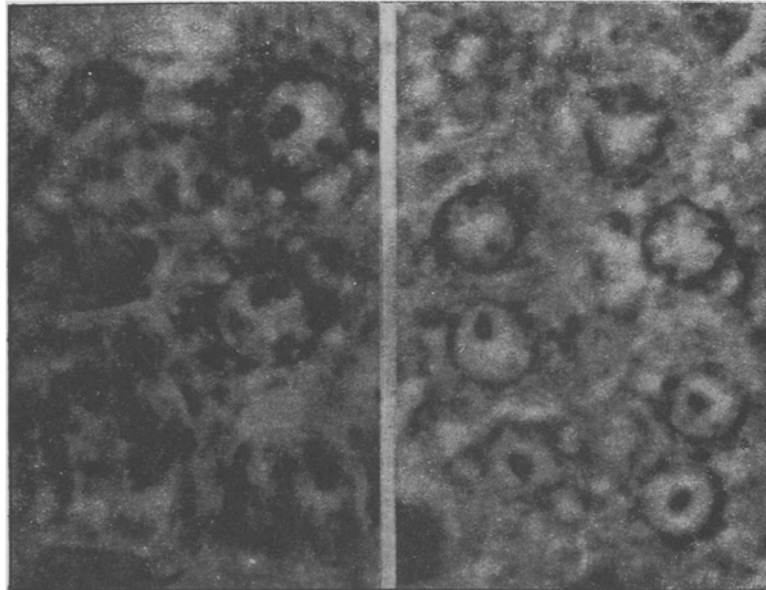


Fig. 1. The nucleic acid content of the liver cells. On the left — control; on the right — after injection of adrenalin.

The results of this series of experiments thus show that the injection of adrenalin in dose causing a fall in mitotic activity cause a fall in the RNA and DNA contents of the cells also.

The reaction of cells of different tissues to the injection of adrenalin is not the same. The sharpest changes are observed in the corneal epithelium and the liver cells; less marked changes in the nucleic acid content are found in the epithelium of the skin and tongue, and in the intestinal epithelium and the lymphocytes of the thymus and lymphatic glands changes are either absent or inconstant and feebly expressed. Comparison of these findings with those on the effect of adrenalin on mitotic activity indicates a quite clear parallel between the changes in the nucleic acid content of the cells and the mitotic activity. Injection of adrenalin causes an obvious antimitotic effect in the epithelium of the skin, the tongue and, in particular, the epithelium of the cornea. In the lymphoid organs adrenalin does not alter the mitotic activity. In the intestinal epithelium the mitotic activity is changed only relatively slightly by the action of adrenalin, and changes are not seen in all the experiments.

In the second series of experiments we investigated the influence of cortisone on the nucleic acid content of the cells. A single injection of cortisone caused an obvious fall in the RNA and DNA contents of the lymphocytes and the thymus and lymphatic glands and in the liver cells. There was an insignificant fall in the nucleic acid content of the epithelium of the cornea and skin. No changes were observed in the RNA and

DNA content of the cells of the intestinal epithelium. Similar findings were obtained after two injections of cortisone. A very severe fall in the nucleic acid content of the lymphocytes of the thymus and lymphatic glands and of the liver cells was observed after repeated injections of the drug. The basophilic clumps and rods, characteristic of the normal cells, disappeared from the cytoplasm of the liver. Only a small perinuclear area of the cell and a narrow border of cytoplasm adjacent to its membrane gave a reaction for RNA (Fig. 2). In the intestinal epithelium there was no change in the RNA and DNA contents of the cells even after repeated injections of cortisone.

The results of the experiments with cortisone thus show that the injection of this drug causes a fall in the nucleic acid content of the cells.

In both the adrenalin and cortisone experiments a quite clear parallel is observed between the mitotic activity and the changes in nuclear metabolism. Cortisone suppresses mitotic activity mainly in the lymphoid organs. Cortisone does not alter the mitotic activity in the intestinal epithelium [1, 3]. The liver occupies a peculiar position, for in adult animals no mitoses are present there.

In regeneration, however, when proliferation of liver cells takes place, cortisone then has a quite considerable antimitotic effect [15].*

In experiments in which cortisone was injected, besides studying the changes in the nucleic acid content, we measured the size of the liver cells. These measurements, carried out by A. N. Chizhova, showed that under the influence of cortisone a marked diminution takes place in the dimensions of the cells and their nuclei, and there is an obvious shift of the variational curves to the left. These measurements suggest that under the influence of cortisone there is not only a relative fall in the concentration of RNA and DNA, as some authors suggest [8], but a true fall in the nucleic acid content of the cell. Thus in spite of the inconsistency of the results of the biochemical investigations dealing with the effect of cortisone on nuclear metabolism [12-14] and others], we may conclude that cortisone causes interference with the synthesis of RNA and DNA in the cell.

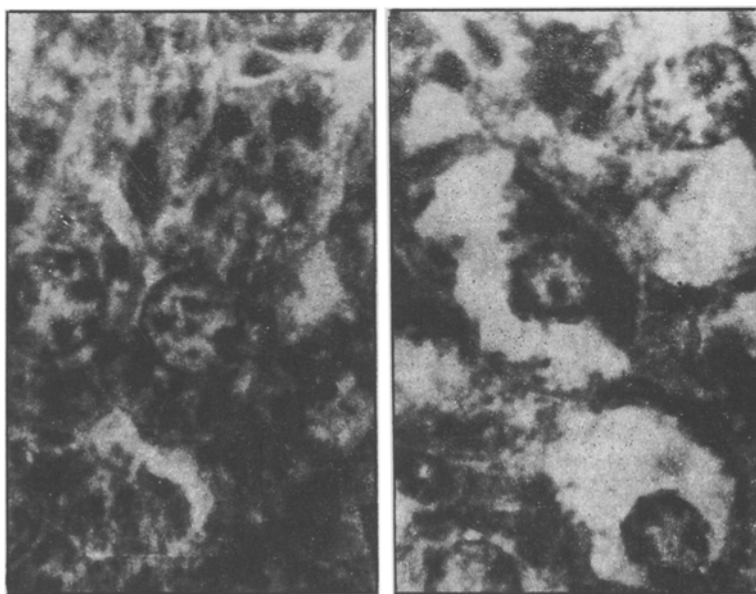


Fig. 2. Nucleic acids in liver cells. On the left — control; on the right — after injection of cortisone.

The results of the experiments performed show that both adrenal hormones, possessing a powerful anti-mitotic action, reduce the RNA and DNA contents of cells. Considering the role of nuclear metabolism in the process of mitotic division, it may be supposed that the antimitotic action of adrenalin and cortisone is connected with interference with the synthesis of nucleic acids. Naturally the influence of the adrenal hormones on nuclear metabolism may be effected not directly, but through other intermediate metabolic links. In one way or another the results of our experiments suggest that adrenalin and cortisone influence cell division

*As in original.

ultimately through nucleoprotein metabolism. Later experiments will show whether this mechanism extends to other neurohumoral factors concerned in the regulation of cell division in the animal body.

SUMMARY

Administration of adrenalin reduces the mitotic activity and considerably changes the content of nucleic acids in the cells. Adrenalin decreases the content of RNA and DNA in the cornea epithelium, hepatic cells and, to a lesser degree in the skin and tongue epithelium. Cortisone reduces the quantity of nucleic acids in the lymphocytes of the thymus gland, in the lymph nodes and hepatic cells. The antimitotic effect of the adrenal gland hormones is evidently connected with the disturbed cellular synthesis of the RNA and DNA.

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*In Russian.

**Omissions as in original. — Publisher.