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HYPOTHALAMIC CHANGES IN RENAL HYPERTENSION

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Introduction

Apart from being the principal organ which governs vegetative functions, the hypothalamus is the site of subcortical centres and forwards cortical impulses toward the periphery. Scharrer and Gaupp (1928) observed groups of cells in the supraoptic and paraventricular nuclei of the hypothalamus which showed signs of endocrine secretion. This led them, in contradiction to Collin and Gersch, to the conclusion that the hormones thought to be produced in the posterior lobe of the pituitary originated, in reality, from the said hypothalamic cells, and passed from here to the neurohypophysis. This conclusion may be regarded as the birth of the concept of neurosecretion.

Detailed investigations concerning neurosecretion started after Bargmann (1949) had observed that Gomori's chromhaematoxylin-phloxine ("Gomori's stain" in the following) was a stain eminently suited for the demonstration of neurosecretory processes [1, 2, 3, 20, 21]. Such processes were thereafter studied in the hypothalamus and the posterior pituitary under physiological conditions and different pathologic states [20, 21, 22, 27, 28, 30]. A number of authors published reports on the neurosecretion and the action of its fractions, *viz.* that of the antidiuretic hormone (ADH) on the kidney, that of vasopressin on blood pressure, and that of oxytocin on the smooth muscles of the uterus [4, 24].

Wide as the range of these investigations was, they yielded unequivocal results only in some respects (*e. g.* concerning the ADH), while a number of problems is still unelucidated.

The present experiments were designed to study possible changes of the neurosecretion in the hypothalamic nuclei in cases of renal hypertension, bearing in mind that the pressor agent vasopressin is produced exactly in the hypothalamus.

Material and method

We used 88 albino rats of the same strain. Their body weight was between 150 and 250 g. Parabiotic pairs were formed (Fig. 1) by uniting the skin of two animals in its entire length, making coeliac anastomoses and applying scapular sutures. Hypertensive surgery, as described by Lőrincz and Gorácz [30] (called "operation H. T." in the following), was performed on

the 4th day of parabiosis on the left-side animal of the parabiotic couple (to be called "animal A" in the following). The operation in question consists in that the kidneys are enclosed in a mildly stretched rubber capsule which increases intrarenal pressure and so induces renal ischaemia. This is the quickest known method for the elevation of blood pressure. Animals so treated developed the histological picture of malignant hypertension within a couple of days. We performed operation H. T. on the fourth day of parabiosis, being known that 3 to 4 days are necessary for capillary communications to develop between parabiotically united animals. Coincidentally with operation H. T., unilateral nephrectomy was performed on the right-side animal of the parabiotic couple (to be called "animal B" in the following). It has been observed [28] that the blood pressure of the two animals follows a parallel course in such cases. The animals received only dry food after the operations and, in addition, 4 ml of milk per day in order to keep their water uptake at a standard level.

Five pairs of parabiotically united animals served as controls. They were kept on the same regime but were not subjected to operation H. T.

We determined blood pressure by means of a photoelectronic instrument as described by GÁTI, WEISZ and RÓZSA [29]. To do so, we anaesthetized the animals by means of intraperitoneally administered 3 mg per 100 g of pentobarbital.

After decapitating the animals, their brain was fixed in Bouin's fluid, embedded in methylbenzoate celloidin, after which we prepared 5 μ serial sections in the frontal plane and dyed them with Gomori's stain (as modified by Bargmann).

Results

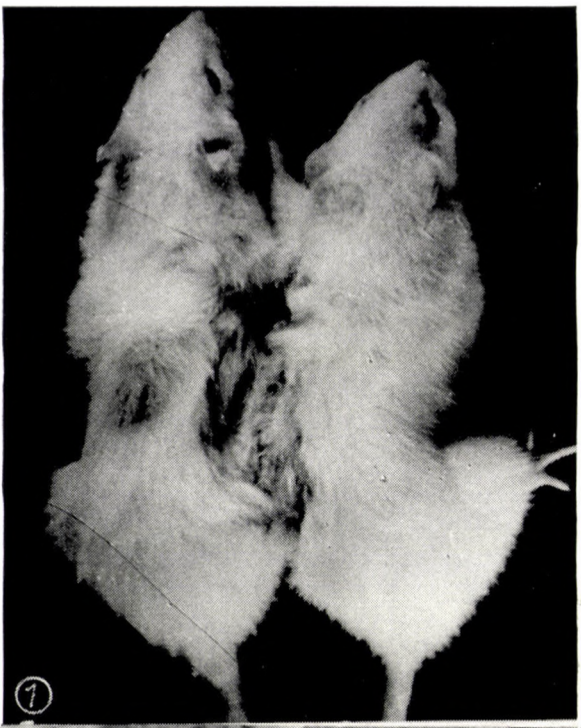
We observed the controls for 6 days after their parabiotic union. The fluctuation of their blood pressure remained within ± 15 mmHg. They were sacrificed on the 6th day and subjected to histological analysis.

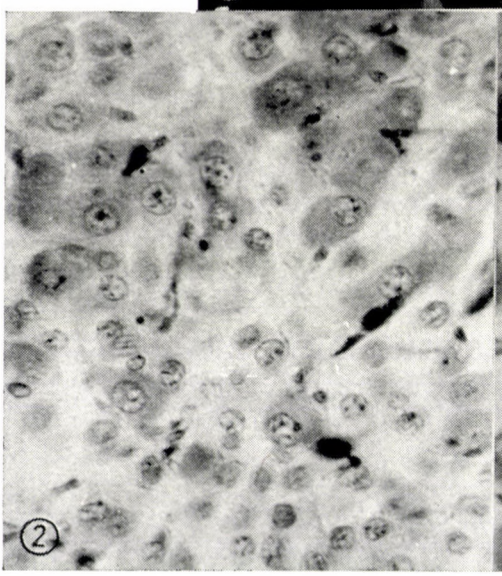
Fourteen parabiotically united couples were used in the first group of experiments. Operation H. T. was performed on the animals A, and unilateral nephrectomy on the animals B on the 4th day of parabiosis. Four couples died in consequence of the operations, and two additional couples were discarded on account of their poor condition. Blood pressure in the remaining 8 couples rose, on the average, from 118 to 154 mmHg on the first postoperative day. There was no essential difference between animals A and B in this respect. After having measured the blood pressure we killed the animals for histological analysis.

We performed the operations on 25 pairs of animals in the second group of experiments. Seven were lost in the course of surgery, and four couples were excluded from the experiment. Blood pressure in the remaining 14 couples rose from an average of 124 to one of 185 mmHg two days after the operation. There was no essential difference between A and B. The animals were sacrificed two days after the operation and worked up histologically.

Treated with Gomori's stain, the ganglionic cells of the supraoptic and paraventricular nuclei revealed delicate, powderlike, evenly distributed bluish-black granulation in the control animals. Both types of nuclei contained Gomori-negative cells as well. It was in the form of Herring's bodies that extracellular Gomori-positive matter (Figs. 2, 3) was found.

We observed a considerable accumulation of Gomori-positive matter in the supraoptic and paraventricular nuclei of the animals used in the first





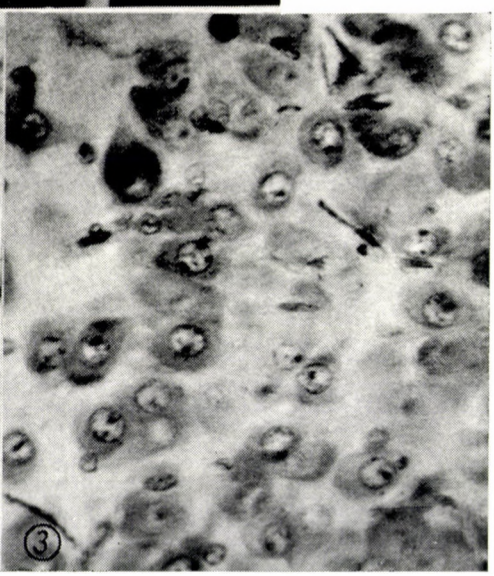


Fig. 1. Parabiotic animals

Fig. 2. Supraoptic nucleus of control rat. Gomori's stain. ×400. Note powderlike, evenly distributed granulation of cells

Fig. 3. Paraventricular nucleus of control rat. Gomori's stain. ×400. Note evenly distributed granulation of cells

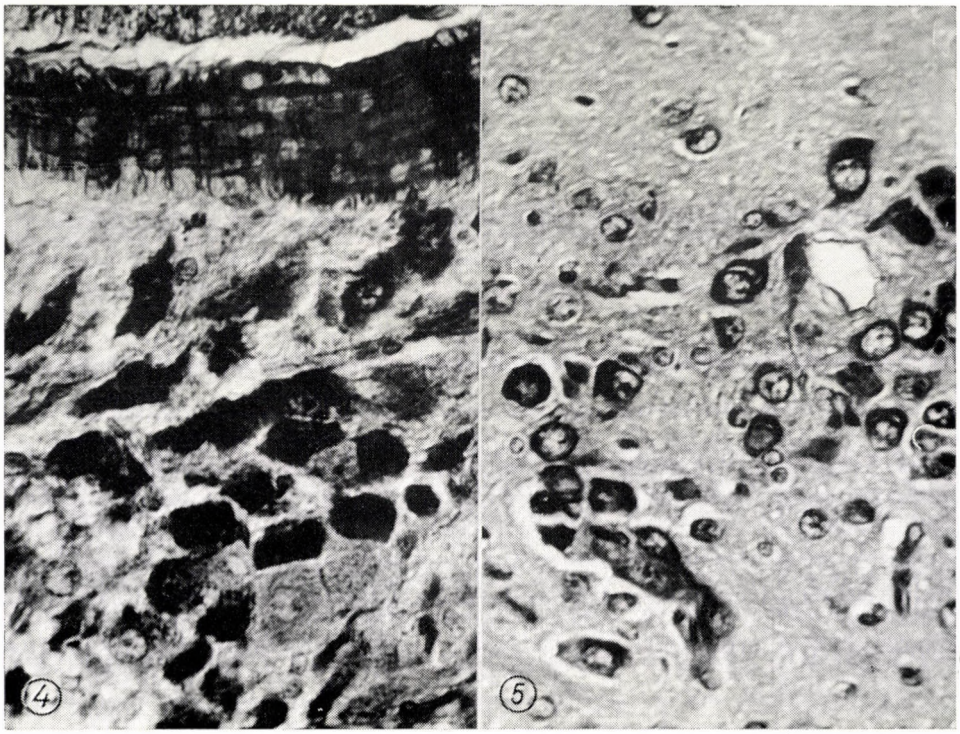


Fig. 4. Supraoptic nucleus at a blood pressure of 150 to 160 mmHg. Gomori's stain. ×400. Note accumulation of Gomori-positive substance

Fig. 5. Paraventricular nucleus at a blood pressure of 150 to 160 mmHg. Gomori's stain. ×400. Note accumulation of Gomori-positive substance

group of experiments, *i. e.* those with a tension between 150 and 160 mmHg (Figs. 4, 5). There were, however, cells in both types of nuclei the cytoplasm of which contained either no or only very sparsely distributed secretion. The amount of extracellular Gomori-positive matter was very small, and the capillaries were markedly dilated. Animals A and B seemed to be histologically similar.

As regards the second experimental group, *i. e.* the animals with a blood pressure between 180 and 190 mmHg, the cells of the supraoptic nucleus seemed to be enlarged, their vacuolated cytoplasm was depleted of secretory granules and showed occasional signs of degeneration. Only a few secretory granules were seen outside of the cells (Fig. 6). The paraventricular nucleus was less hypertrophic than the supraoptic area, nor were the cells here completely empty. While secretion appeared in the paraventricular nucleus of the animals of the first experimental group (150 to 160 mmHg) in the form of diffuse granulation, in this group it was situated at the edge of the cytoplasm and sur-

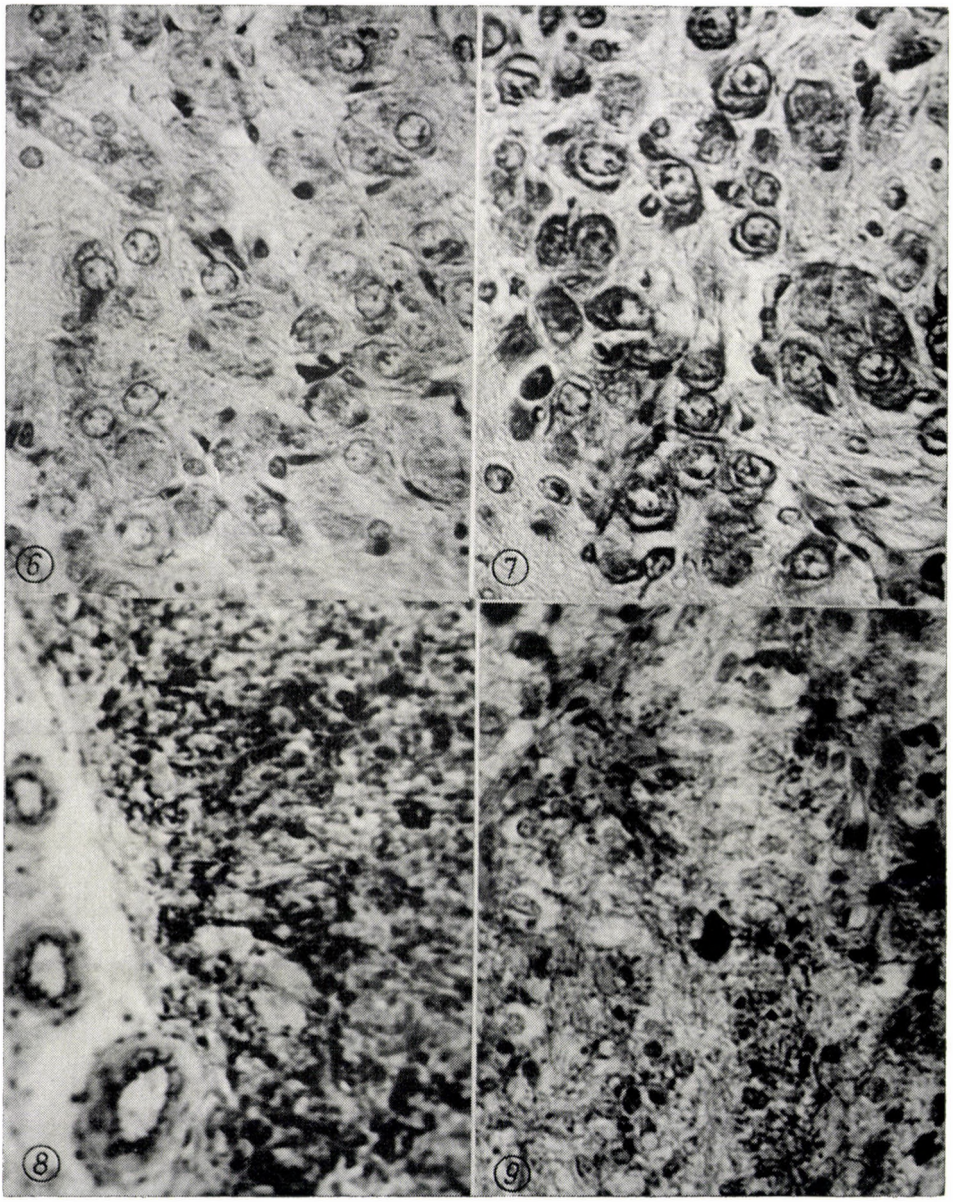


Fig. 6. Supraoptic nucleus at a blood pressure of 180 to 200 mmHg. Gomori's stain. ×400. The cells are enlarged, their cytoplasm lacks secretory granules

Fig. 7. Paraventricular nucleus at a blood pressure of 180 to 200 mmHg. Gomori's stain. ×400. Granules of secretion form a crescent at the edge of the cytoplasm. Note extranuclear vacuolization at several points

Fig. 8. Neurohypophysis of control rat. Gomori's stain. ×400. Note great amount of Gomori-positive substance in the form of granules or clods

Fig. 9. Neurohypophysis of test animal. Gomori's stain. ×400. The secretion has disappeared, and the pituicytes are well distinguishable against their background

rounded the nucleus in the form of a ring or crescent (Fig. 7). Most cells revealed extranuclear vacuolization. Many extracellular secretory granules were seen. There was no essential histological difference between animals A and B.

A great amount of Gomori-positive substance was found in the neurohypophysis of the controls. It appeared in the form of fine granules or coarse clods (Fig. 8). In contradistinction, the neurohypophysis in both experimental groups revealed morphological signs of hyperfunction (Fig. 9). The secretion had disappeared, the pituicytes were enlarged and, protruding from their background, were well visible; the capillaries appeared to be strongly distended.

Both members of the test pairs offered this hypothalamic picture, and also hypertension was present in both of them.

No such phenomena were observed in the controls.

Discussion

Investigations into the interrelations between renal hypertension and neurosecretion are made difficult by the fact that the surgical intervention carried out to induce renal hypertension is inevitably accompanied by a change in renal function so that it is not easy to tell whether phenomena observed in the hypothalamus are due to elevated blood pressure or an impairment of the renal functions. The animals B had undamaged kidneys, and their blood pressure was raised without any change in renal function so that this factor of disturbance could be disregarded.

Literature contains few reports on investigations into the relationship between neurosecretion and hypertension, and even the few existing data have but a questionable value because many of the problems connected with hypertension are still unelucidated. The difficulty is further augmented by the fact that the neurosecretion contains vasopressin, while the kidney also produces a pressor substance, namely renin: both agents have more or less the same effect and their demonstration is extremely laborious [7, 10, 14, 17, 18, 19].

The results of our experiments allow the conclusion that there exists an interrelation or parallelism between the action of the two pressor agents, the hypertensive state induced by the kidney's increased production of renin (presumably made irreversible after some time by other factors) and — finally — the changes observable in the hypothalamus.

This theory seems to be supported by a number of literary data. Posterior pituitary extract provokes renal ischaemia and degeneration [7]. Increased production of vasopressin, provoked by a stimulation of the diencephalon, or the intravenous administration of vasopressin leads to an elevation of the blood pressure and increased peripheral resistance, *i. e.* to symptoms characteristic of acute nephritis [17].

Apart from basophilia, a hyperfunction of the posterior pituitary, further the accumulation of antidiuretic substances in the blood were observed by ANSELMINO and HOFFMANN, and also by BÜTTER, in connection with hypertension [4]. In the cerebrospinal fluid of hypertensive animals MIASNIKOV found pressor agents (pitressin), which must have gained access to the cerebrospinal fluid via the infundibulum and the third ventricle. HAYLE and LANG [4] could not support this hypothesis.

We venture to suggest that renal hypertension is maintained or made permanent by a Gomori-positive substance of hypothalamic origin, or some antidiuretic or pressor or another unknown component thereof, which acts either as a hormone or via the nervous system.

Summary

Processes of neurosecretion have been studied in parabiotic hypertensive rats, on the evidence of changes observed in their hypothalamus and the posterior pituitary lobe.

(1) Hypertension of 150 to 160 mmHg was accompanied by an accumulation of neurosecretion in the supraoptic and paraventricular nuclei.

(2) When hypertension rose to 180—190 mmHg the cells became enlarged in the said hypothalamic nuclei, their cytoplasm was drained of secretory granules and the cytological picture showed increased neurosecretory activity.

(3) The posterior pituitary contained no secretion in either case.

It is suggested that the observed changes in neurosecretion were connected with the experimentally induced renal hypertension.

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ИЗМЕНЕНИЯ ГИПОТАЛАМУСА ПРИ ПОЧЕЧНОЙ ГИПЕРТОНИИ

Б. АРОШ и М. ЭРТЛ

Авторы на основании изменений гипоталамуса и задней доли гипофиза исследовали нейросекреторную деятельность гипертонических крыс, сшитых в парабиоз. Было установлено, что

1. При гипертонии в 150—160 мм Hg в **nucleus supraopticus** и в паравентрикулярных ядрах накопляется нейросекрет.

2. При гипертонии в 180—190 мм Hg в указанных ядрах гипоталамуса клетки увеличиваются, из плазмы исчезают зернышки секрета и картина клеток показывает повышенную продукцию нейросекрета.

3. В задней доли гипофиза в обоих случаях не было секрета.

На основании полученных данных авторы предполагают, что указанное изменение секреторной деятельности связано с экспериментально вызванной почечной гипертонией.

HYPOTHALAMUSVERÄNDERUNGEN BEI RENALER HYPERTONIE

B. AROS und M. ERTL

Die Neurosekretionsprozesse von parabiotischen hypertonischen Ratten wurden im Hypothalamus und Hypophysenhinterlappen untersucht. Es wurde folgendes beobachtet:

1. Bei Hypertonie von 150—160 mm Hg sammelt sich das Neurosekret im Nucleus supraopticus und paraventricularis an.

2. Bei Hypertonie von 180—190 mmHg vergrößern sich die Zellen in diesen Hypothalamuskernen, die Sekretgranula verschwinden aus dem Plasma, und die Zellen zeigen gesteigerte Neurosekretproduktion.

3. Der Hypophysenhinterlappen war in beiden Fällen sekretfrei.

Auf Grund der Resultate wird angenommen, daß diese Veränderungen des Neurosekretionsprozesses mit der experimentell herbeigeführten renalen Hypertonie zusammenhängen.

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