NEUROSECRETION IN THE HYPOTHALAMIC NUCLEI AND THE CHANGES IN THE CONCENTRATION OF THYROID HORMONE

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Previously we have related the cytological changes in the secretory nuclei of the hypothalamus of the white rat to the concentration of thyroid hormone in the body. It has been shown that an increased concentration of thyroid produced by a daily injection results in an intense formation of neurosecretion and subsequent functional exhaustion of the neurones. Prolonged injection of 6-methylthiouracil delays the initial stages of the neurosecretory cycle and leads to the deposition of an active substance in the secretory neurones [2].

Here we have set out to determine the influence of changes of thyroid concentration on the formation and liberation of the neurosecretion, and on its distribution within the hypothalamo-hypophysial system.

EXPERIMENTAL METHOD

The work was carried out on 36 rabbits of both sexes weighing from 1.5 to 2.5 kg; the thyroid was removed from 15 animals. After one month eight of the animals recieved 30 mg/kg thyroxin. At the same time two groups of intact rabbits (seven in each group) received the same amount of thyroxin or 45 mg/kg 6-methylthiouracil. The preparations were given twice per day for ten days by mouth in the form of a suspension in 2% starch. Seven rabbits were kept as a control group. Histological studies were made of the hypothalamus and hypophysis, which were fixed in Bouin's fluid. Tests for RNA by Brachet's method were made, as well as special tests for neurosecretion (aldehyde-fuchsin by Gabu's method and counterstaining with hematoxylin, or with Helmi's mixture, or by Gomori's chrome-quartz hematoxylin. Thyroid glands taken at operation, or after death were fixed in 10% formalin, embedded in paraffin, and stained in hematoxylin-eosin.

EXPERIMENTAL RESULTS

In rabbits the topography of the secretory hypothalamic nuclei (supra-optic and paraventricular) bears some resemblance to the arrangement of the corresponding nuclei in puppies, as we have described previously [3]. The dilated portion of the paraventricular nucleus which is pear shaped lies up against the ependyma of the III ventricle, and the narrow portion is directed laterally and downwards towards the optic tract (Fig. 1a). The large neurones of this nucleus are as a rule scattered, and at a considerable distance from each other; only certain of the cells are arranged in groups of three or four. The region of the nucleus is well vascularized, and it can be seen that there is a close contact between the bodies of the neurones and the blood capillaries. The cells contain an aldehyde-fuchsin substance which takes the form of a fine granularity surrounding the nucleus. In the peripheral zone of the cells there are two or three large clumps of this substance (Fig. 1b). The movement of the secretion along the outgrowth can be followed in some of the preparations; when secretion is present in them the outgrowths have the appearance of bristles or of ribbon-like strips running between the neurone.

The supra-optic nucleus lies in front of the optic chiasma. Its neurones are of the same size as the cells of the paraventricular nucleus, but they are more compactly arranged. The narrow cell cord continues from the base of the group dorsally above the chiasma, but does not enclose it entirely. Caudad to the chiasma there are scattered neu-

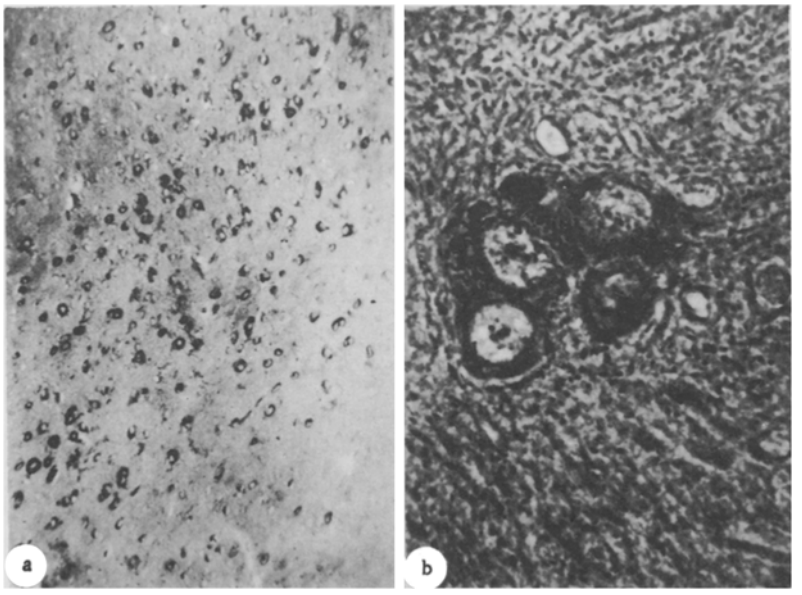

Fig. 1. Paraventricular nucleus of rabbit. a) General appearance of nucleus; magnification 100 x; b) clumps of secretion in the neurones. Magnification 1200 x.

rones containing granules of a secretion; the compact group of cells which we observed in this zone of the hypothalamus in puppies, is absent from rabbits. The neurones of the supra-optic nucleus are mostly spindle-shaped and contain a large number of fine secretory granules. In the dorsal portion of this nucleus there are small elongated cells having a dark pycnotic nucleus and a cytoplasm which is completely filled with secretion. These cells have been described in the preoptic nucleus in fish and amphibia as degenerate forms, or as representing a holocrine type of secretion [1, 4].

Caudad to the optic chiasma the hypothalamo-hypophyseal tract is formed from axons descending fan-wise and passing into the ventral wall of the infundibulum, and then through the short hypophyseal stalk to the posterio hypophyseal lobe. In the wall of the infundibulum the tract fibers are evenly arranged throughout its whole thickness from the ependymal cells to the boundaries with the tuberal portion of the adeno hypophysis. Blood vessels which penetrate into the wall of the infundibulum as loops divide it transversely, and are surrounded by the axons of the hypothalamo-hypophyseal tract. The neurosecretion is scattered along the length of the tract in the form of small granules or clumps, or else it is concentrated in the form of small spheres having a granular structure (Herring bodies); such are the morphological appearances of the secretion in the hypophyseal stalk. The descending portion of the III ventricle which penetrates into the hypophyseal stalk is lined with flattened and loosely arranged ependymal cells which affords favorable circumstances for the penetration of the neurosecretion into the fluid in the ventricles.

In the posterior hypophyseal lobe the secretion accumulates chiefly in the form of a fine diffuse granularity. When there is a considerable increase in the amount of secretion in the posterior lobe, Herring bodies can be seen. There is an uneven distribution of the secretion between the hypothalamus and hypophysis. In each control animal the main portion of the secretion was concentrated either in the neurones of the nuclei, or in the walls of the infundibulum, or in the posterior hypophysial lobe. The impression is gained that the secretory process takes place phasically: the phase of formation of secretion in the neurones gives way to one in which the cells are emptied and the secretion passes into the distal parts of the neurohypophysis.

In animals which had received thyroxin, the morphological changes in the thyroid gland show up as a state of hypofunction. In the hypothalamo-hypophysial system of such animals there is an increase in the amount of neurosecretion. In the cells of the paraventricular and supra-optic nuclei the secretory granules are distributed throughout the whole neuroplasm; large clumps are not present, apparently because of the rapid flow of secretion. Ribonucleoproteins themselves become smaller than in the control animals. From the supra-optic nuclei the secretory

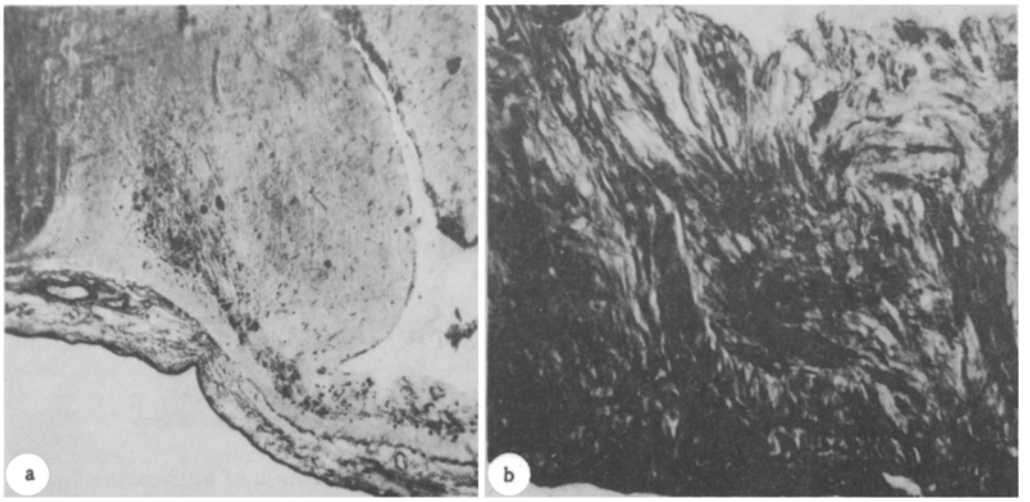

Fig. 2. Abundant secretion in the supra-optic-hypophysial tract of a rabbit treated with thyroxin; magnification 100 ×; b) clumps of secretion between vessels penetrating into the median eminence. Magnification 1200 ×.

substance takes two directions. Besides the flow towards the hypothalamo-hypophysial tract, which occurs in the control animals also, a movement of the secretion can be seen along axons directed towards the dorsal regions of the hypothalamus. In the supra-optic nucleus, when thyroidine is injected, an abnormally large number of degenerating cells can be found. In the hypothalamo-hypophysial tract, besides the small granules lying along the course of the axons there are a larger number of homogenous granular spherical bodies (Fig. 2a). An increase in the amount of neurosecretion in the wall of the infundibulum is associated with a considerable dilatation of the vessels which pass through the funnel at right angles to its length (Fig. 2b). In the Pituitary stalk and in the posterior hypophysial lobe the amount of secretion is also increased (Fig. 3). In animals of all the experimental groups penetration of certain secretory granules into the intermediate lobe of the hypophysis could be made out. When the animals were injected with thyroxin the perivascular migration of the neurosecretion could be seen still more clearly. In some of the preparations the passage of a large amount of secretory material along the course of the vessels and of the connective-tissue layers into the depth of the intermediate lobe could be seen.

The injection of 6-methylthiouracil leads to a reduced production of secretion and to a reduction in the number of its granules in the neurohypophysis. The influence of 6-methylthiouracil on rabbits shows some individual variations and there is a characteristic goiterous reaction of the thyroid gland, which varies in degree. The reduction of intensity of the secretion in the hypothalamic nuclei and the development of the goiterous reaction was directly related. In the secretory neurones the amount of specific granularity is reduced; in the paraventricular nucleus this phenomenon is more marked than it is in the supra-optic nucleus. At the same time the amount of RNA and Nissl substance in the cells becomes less. The total amount of neurosecretion in the tract, infundibulum, and posterior hypophyseal lobe is reduced. The store of secretory substance in the posterior lobe begins to fall first of all in the periphery bordering the pars intermedia. However in some animals, in certain parts of the neurohypophysis a secretion is present which may be what has been left over from the secretory cycle preceding the action of 6-methylthiouracil. In such cases there is an alteration to the staining properties of the neurosecretion, and the Herring bodies and small granules are weakly stained by aldehyde-fuchsin and lose their clear outlines. One gets the impression that the secretion is being rapidly dispersed not only in the posterior hypophyseal lobe but also by passage through the median eminence.

In rabbits which were killed 40 days after thyroidectomy changes in the neurosecretion were of various types. In some there was a marked reduction in the amount of neurosecretion in all parts of the hypothalamo-hypophysial system, and in others specific granules were present in the neurones when there was only a very small amount of secretion in the neurohypophysis. In the operated animals which received thyroxin for 10 days, the production of the neurosecretion was to some extent enhanced. There was an increased amount of secretion in the posterior hypophyseal lobe and in the wall of the infundibulum. Results concerning animals No. 8 in whom the thyroid gland was in-

Fig. 3. A large amount of neurosecretion in the hypophyseal stalk of a thyroxin-treated rabbit. Magnification 400 ×.

completely extirpated are particularly interesting. In the remaining small parts of both lobes ($^1/_8$ of a lobe) 40 days after the operation there was an increased regeneration of follicular cells, and a marked hyperplasia of the epithelium at parts remote from the follicular damage. The sum total of the compensatory processes appeared to result in an elimination from the organism of the hormonal insufficiency, because the intensity of neurosecretion in this animal was as well developed as it was in the intact rabbit.

The results we have obtained indicate that the secretory nuclei of the hypothalamus react to a change in the concentration of thyroid hormone in the body. The injection of thyroid for ten days, in the dose that we used led to an increase in the amount of secretion in the hypothalamo-hypophyseal system. With the injection of 6-methylthiouracil the production of secretion in the hypothalamic neurones was reduced and there was a fall also in the amount in the neurohypophysis. Thyroidectomy led to a suppression of secretion, which was somewhat reduced by the injection of thyroidine.

Similar results were obtained by Shiozaki [7] in experiments in which a stimulating influence on the neurosecretion of rats was observed to follow a single injection of thyroidine. Increasing the amount of thyroxin in fish also caused an accumulation of neurosecretory material in the wall of the infundibulum [5]. The influence of thyroidine on the hypothalamus is brought about not only by an increase of hormone in the blood. Yamada and Greer [9] showed that when microinjections of thyroxine were made into the anterior hypothalamus or hypophysis the secretion of thyroid hormone was suppressed. Yamada considers that the hypothalamus is a receptor zone, which together with the hypophysis is sensitive to the concentration of thyroid hormone, and that it regulates the circulating level of this hormone [8].

In our investigation the increase of the concentration of thyroxin in the blood of the rabbits led to an increase in the amount of neurosecretory material in all parts of the hypothalamo-hypophysial system. The question now arises as to whether this neurosecretion accumulates as a result of an enhanced production, or whether the accumulation is related to an impaired flow into the neurohypophysis. With intramural injections of thyroxin into the anterior portion of the hypothalamus the increase of triiodothyronine and of thyroxin increases, while the concentration of these hormones in the blood and the factor facilitating the liberation of thyrotropin are reduced [6]. In the light of these results the increased amount of secretion in the neurohypophysis of the rabbits treated with thyroxin appear to result from an insufficient clearance into the blood stream. According to our findings the impairment into the flow of neurosecretion is associated with an increase of its formation in the neurones, as indicated by the enhanced dispersion of ribonucleoproteins and of Nissl substance by the cells of secretory nuclei. Further evidence is the appearance of a new flow of secretion, which is not found in the control animals from the supra-optic nucleus into the dorsal portions of the hypothalamus.

SUMMARY

A study was made of changes in the rate of secretion in the supra-optic and paraventricular nuclei of rabbits in relation to thyroid concentration in the body. Changes in the hormonal balance were induced by thyroidectomy and by the administration of thyroidine or of 6-methylthiouracil.

Hypothalamic secretion in the control animals was fluctuating, i.e., a phase of secretion was followed by one of evacuation and a shift of the secretory granules into the neurohypophysis. Accordingly the main mass of neurosecretion was present either in the cells of the paraventricular and supra-optic nuclei and in the median eminence, or in the posterior hypophyseal lobe.

Treatment with thyroxin for 10 days led to an intensified production of the secretion in the hypothalamic nuclei, and to its accumulation in the neurohypophysis. Thyroidectomy or administration of 6-methylthiouracil decreased secretory activity by the cells, and caused a reduction in the store of neurosecretion in the posterior hypophyseal lobe.

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