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TO STRESS FROM IMMOBILIZATION

B. Gajkowska, A. Luciani and J. Borowicz

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16. Abstract Electron microscopic morphological studies revealed a stimulatory response of the hypothalamus-hypophyseal system of the rat brain to stress produced by immobilization. Total immobilization for two days resulted in changes in the neurons of the supraoptical and paraventricular nuclei and in the fibers of the neurohypophysis indicating an increased production of neurosecretory granules, their rapid flow and enhanced secretion to the blood. Partial immobilization of the animals for 3 weeks produced in turn changes of a somewhat different character and of weaker intensity, which may be considered as a manifestation of the adaptation of the system and of the whole organism to the changed condition.			
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REACTION BY THE RAT HYPOTHALAMUS-HYPOPHYSEAL SYSTEM
TO STRESS FROM IMMOBILIZATION

B. Gajkowska, A. Luciani and J. Borowicz
Laboratory for the Ultrastructure of the Nervous System,
Experimental and Clinical Medical Center, Polish Academy of Sciences, Dr. J. W. Borowicz, Director

The hitherto prevailing view on the regulation of the activity of the hypothalamo-hypophyseal system under stress relies chiefly on results from biochemical and physiological research. The link at the present time with problems of space medicine calls for recognition of the type and scope of changes that occur in the organism under conditions of restricted movement as a function of the degree and duration of the stress factor. /421*

It has been demonstrated, that long-term immobility induces disorders in metabolism and hormonal regulation both in humans and in animals (Kvetnansky et al., 1970; Paul et al., 1971; Reklewska et al., 1972; Tomaszewska, Poczopko, 1972).

On the basis of biochemical research carried out on rats subjected to several weeks of immobility it was found that there was a drop in protein synthesis in the uterus, kidneys, heart and skeletal muscles (Fedorov et al., 1973; Fedorov, 1970, 1973) and a reduction in the overall amino acid content in all tissues amounting to 20% as compared with the norm. Likewise described is a reduction in glycogen content in muscles (Bergström et al., 1967; Baranski et al., 1975) and a decrease shown in heart volume as well as defective carbohydrate metabolism in cardiac ventricles (Prohaska et al., 1973). Long-term immobilization has likewise led to increased diuresis and water intake, although not accompanied by changes in organ fluid distribution (Sobocinska, 1973 a, b).

In the available literature we find reports in a few cases on the

* Numbers in the margin indicate pagination in the foreign text.

subject of the reaction of the hypothalamo-hypophyseal system to stress induced by immobilization (Andrianova, 1971; Sapronov and Ryzhen- /422 kov, 1974) and in consequence the purpose of our work has been to try to grasp the cytophysical changes in the ultrastructure of the neurosecretory hypothalamus of the rat under conditions brought about by short-term but total immobility and also by long-term but partial restriction of movement.

Material and Methods

The experiment was conducted with 28 male Wistar rats, 2 mo old and weighing about 200 g. Two methods were employed for immobilizing the animals:

I. 10 rats were totally immobilized for 2 days by being put in tight wire jackets that eliminated all movement except those barely necessary for feeding;

II. 10 rats were kept for 3 wk in special small cages that reduced their movements to the maximum (it was hard for them to turn even partially around).

Both groups received food and drink ad libitum. The other 8 animals were the control. For electron microscope study segments were taken from the supraoptic nucleus and the paraventricular hypothalamic nucleus and part of the neurohypophysis. The material was preserved in 4% glutaric aldehyde in a phosphate buffer at pH = 7.4 for 1.5 hr and then in 2% OsO_4 for 2 hr. Dehydration was done in increasing concentrations of alcohol and the material immersed in Epone. Ultrafine sections were stained on netting with uranyl acetate and lead citrate. Electron microscope photography was done with a JEM-7A.

Results

1. Electron Microscope Study of Animals Totally Immobilized for Two Days

Supraoptical and Paraventricular Nucleus

In view of the similar character and intensity of observed changes the descriptions given will deal with the neurons of both secretory nuclei.

In all observed cells of the secretory nuclei we find the presence of large cellular nuclei of irregular shape with deep invaginations (Fig. 1, 3). The cellular nuclei are filled with chromatin that is evenly distributed, only at times forming larger concentrations quite close to the nuclear membrane. In the nucleoplasm our attention is drawn to a fairly large number of perichromatin granulations and one or two nucleoles of great electron density, in which the fibrillar and granular portions may be distinguished. /423

In the cytoplasm of the secretory neurons we observe a characteristic arrangement of cellular organelles. In the circumnuclear region there is a highly developed GERL complex with a great number of mature neurosecretory granulations and microvesicles filled with material of different electron density in close proximity to the canals of the Golgi apparatus (Fig. 2, 3). One's attention is also attracted by a rather large number of lysosomes and dense bodies as well as two types of multivesicular bodies, clear and dark (Fig. 1, 3). In many neurons we note likewise dilation of the canals of the Golgi apparatus (Fig. 2, 3) as well as the presence in the narrow canals of an anomalous substance with little electron density. The ergastoplasmic reticulum is located in the peripheral parts of the neuron with fair regularity in the form of numerous elongated narrow canals covered with ribosomes (Fig. 2). The canals are at times short and wide, filled with a small amount of a flocculent substance and covered with a small amount of ribosomes. In the neuron cytoplasm we note a large number of polyribosomes and of oval or elongated mitochondria lying chiefly adjacent to the Golgi apparatus. Typical appears to be the amount of neurotubules of different lengths scattered in the cytoplasm with a certain regularity (Fig. 4).

Neural Portion of the Hypophysis

In the majority of nerve fiber endings in the hypotha-

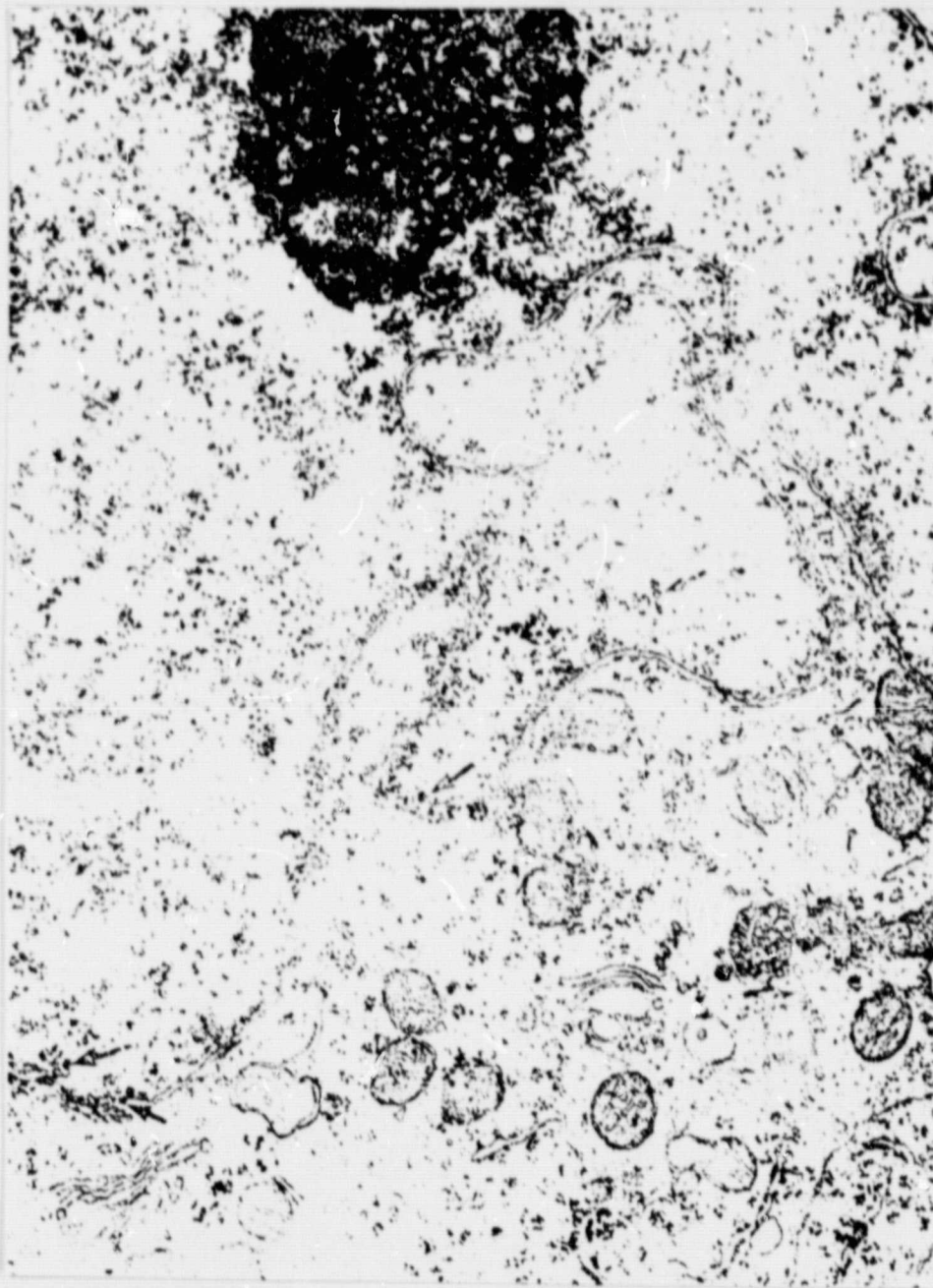


Fig. 1. Two-day complete immobilization. Supra-optic nucleus. Fragment of cell nucleus with deep invaginations. Electron dense nucleolus and numerous perichromatin granules (arrows). In cytoplasm Golgi apparatus, neurosecretory granules, multivesicular bodies and mitochondria. X 28,800.

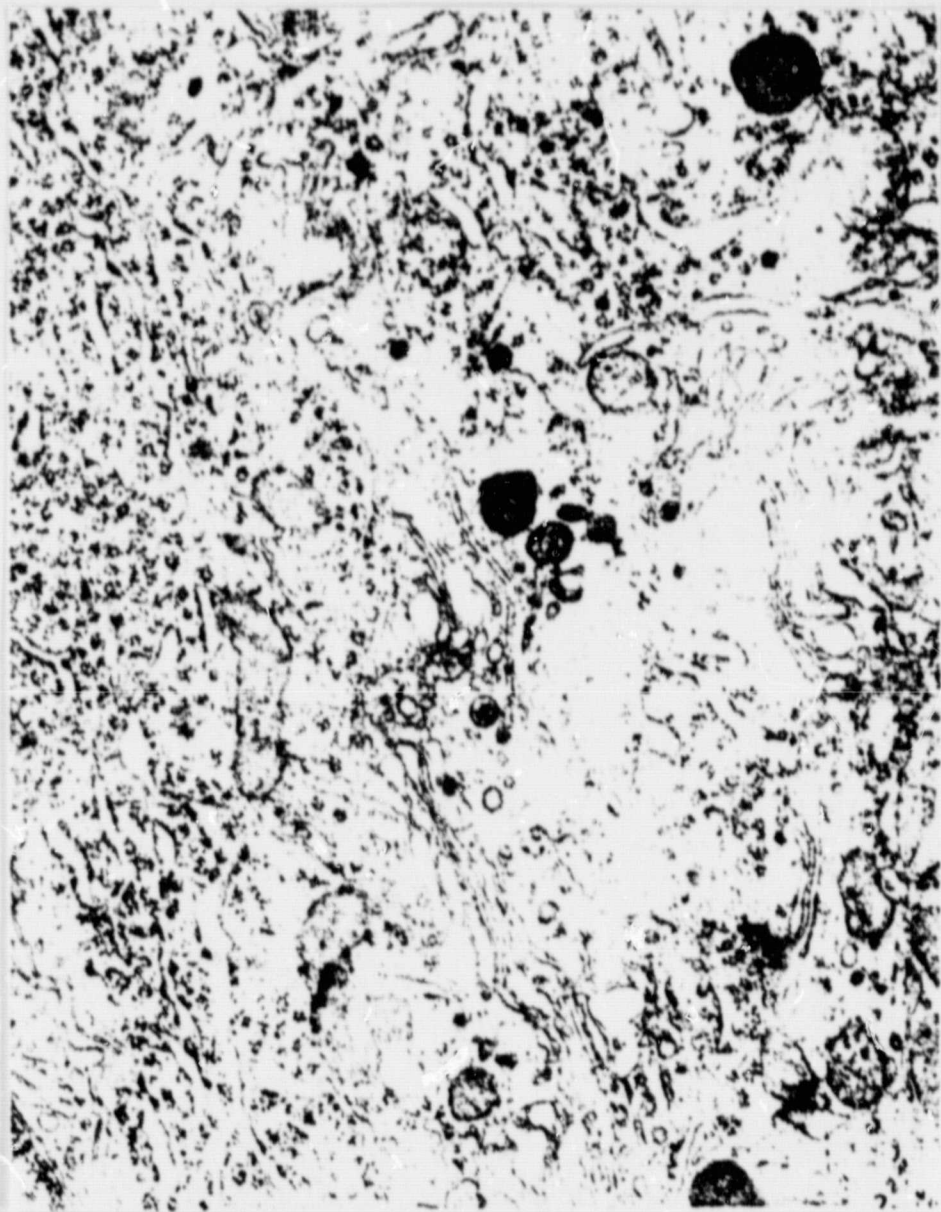


Fig. 2. Two-day complete immobilization. Paraventricular nucleus. In a fragment of cytoplasm well developed Golgi apparatus, numerous neurosecretory granules, dense bodies, lysosomes and well developed ergastoplasmic reticulum. X 28,800.

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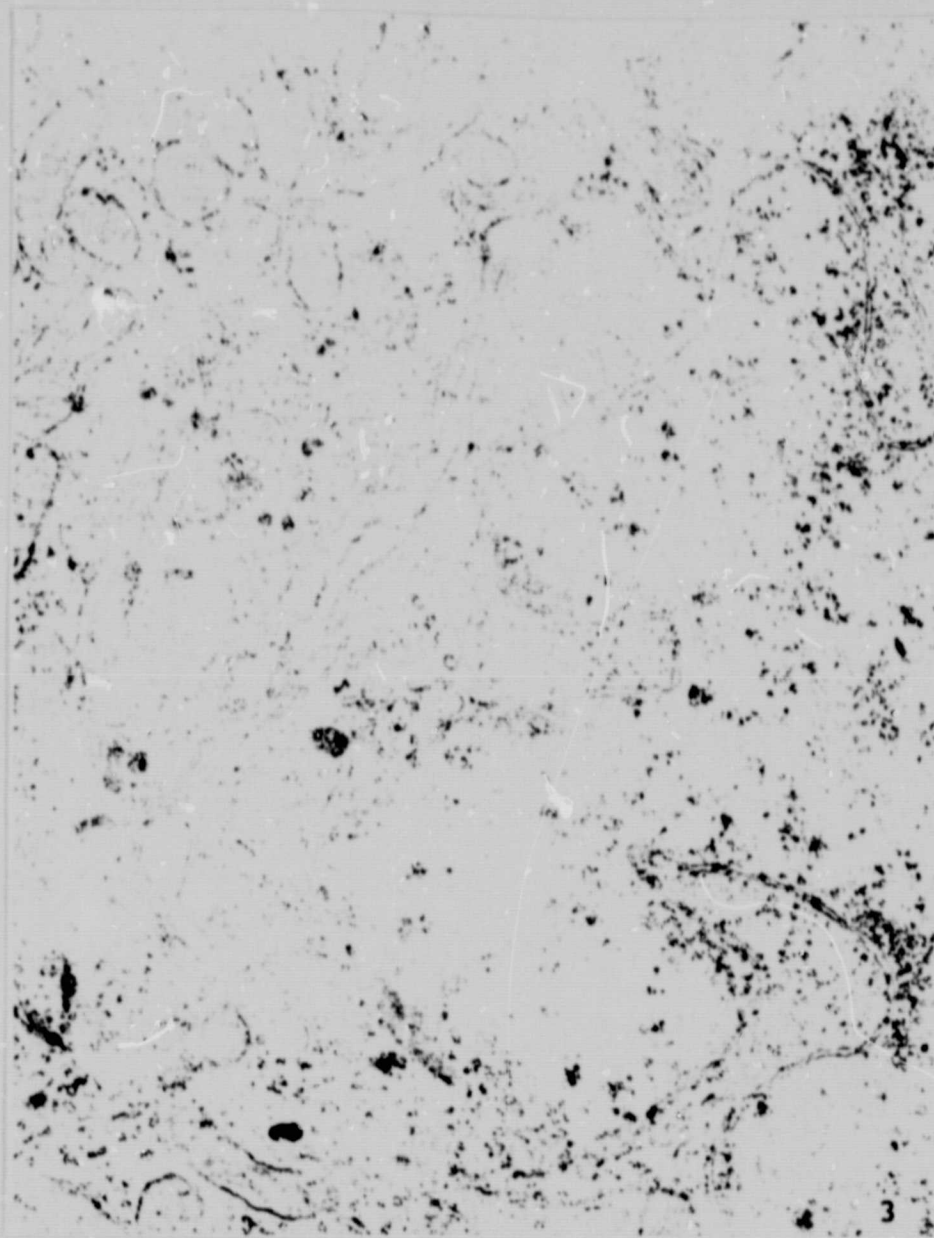


Fig. 3. Two-day complete immobilization. Supra-optic nucleus. Nucleus with deep invaginations. In cytoplasm well developed Golgi apparatus, some of its canals dilated, numerous neurosecretory granules, dense bodies, lysosomes, multivesicular bodies and mitochondria. X 18,900.

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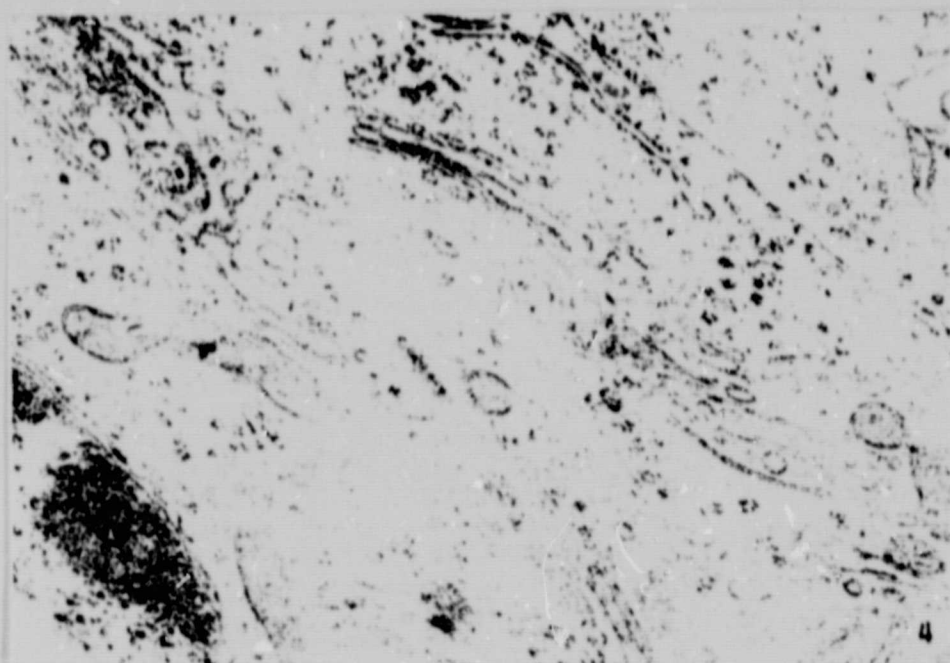


Fig. 4. Two-day complete immobilization. Paraventricular nucleus. Numerous neurotubules in a fragment of cytoplasm. X 26,100.

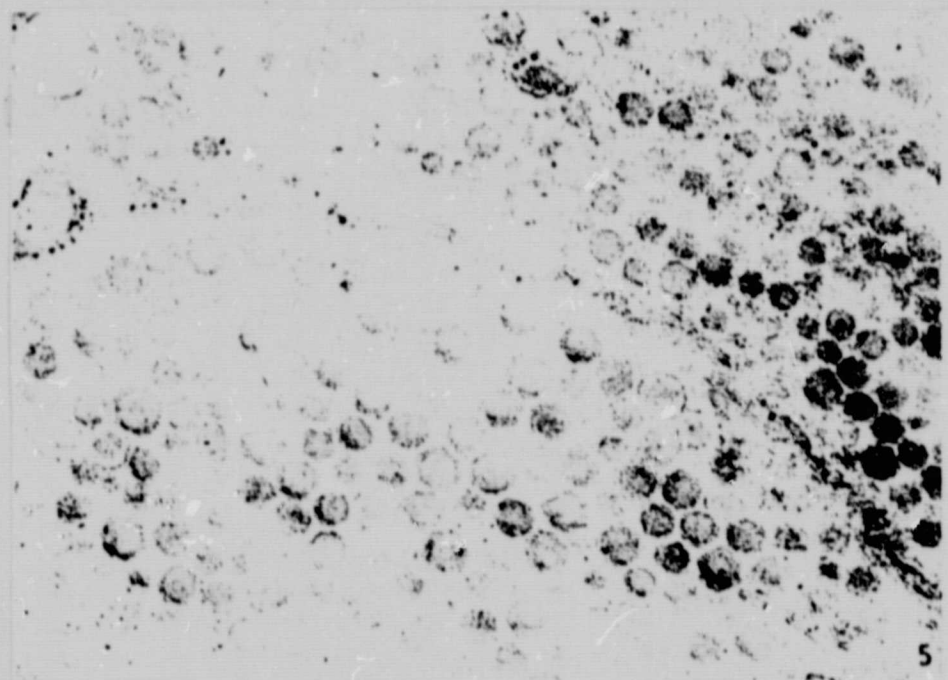


Fig. 5. Two-day complete immobilization. Neurohypophysis. Abundant neurosecretory granules in fibers. X 28,800.

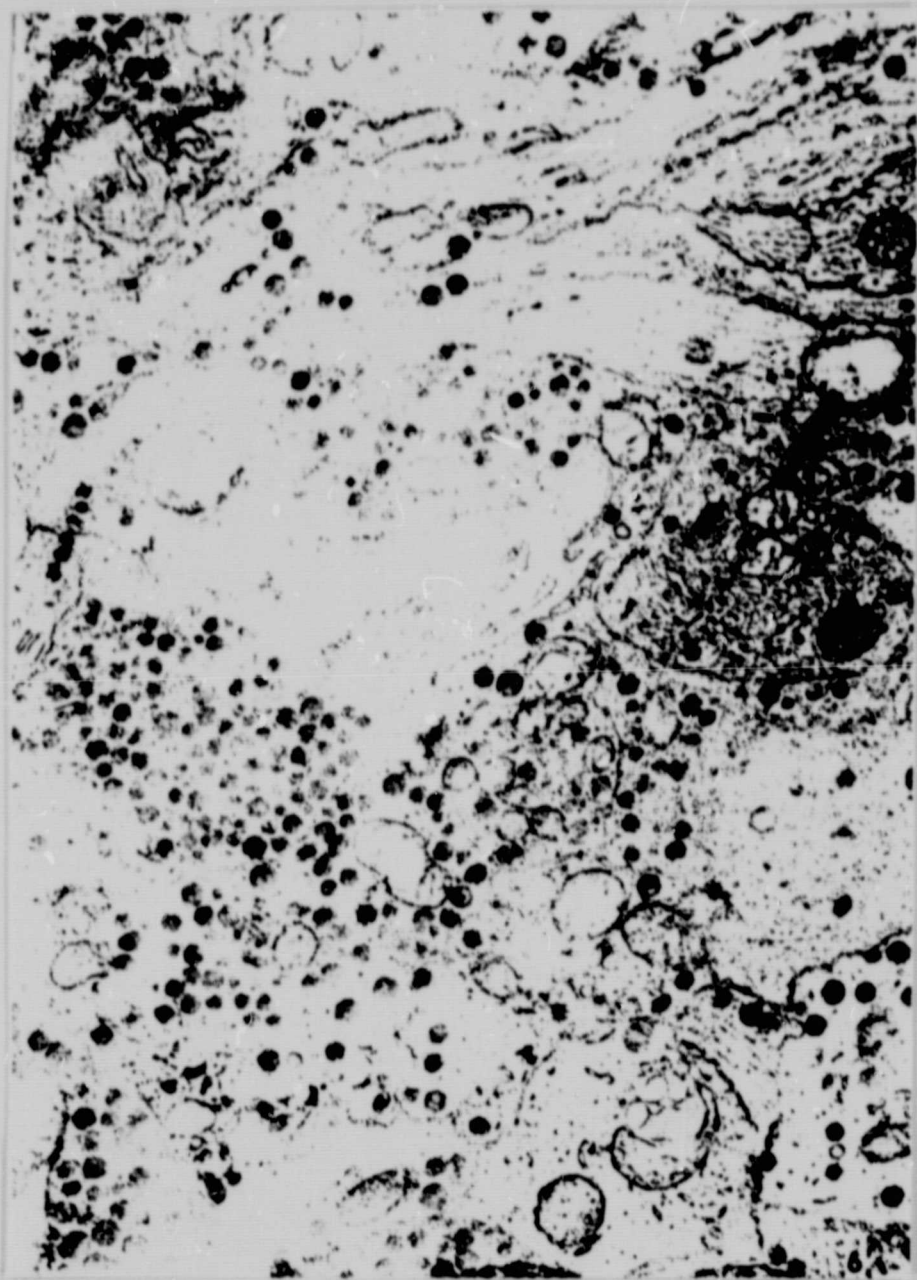


Fig. 6. Two-day complete immobilization. Neurohypophysis. Transverse and longitudinal sections of fibers. Beside neurosecretory granules, microvesicles and neurotubules. X 13,500.

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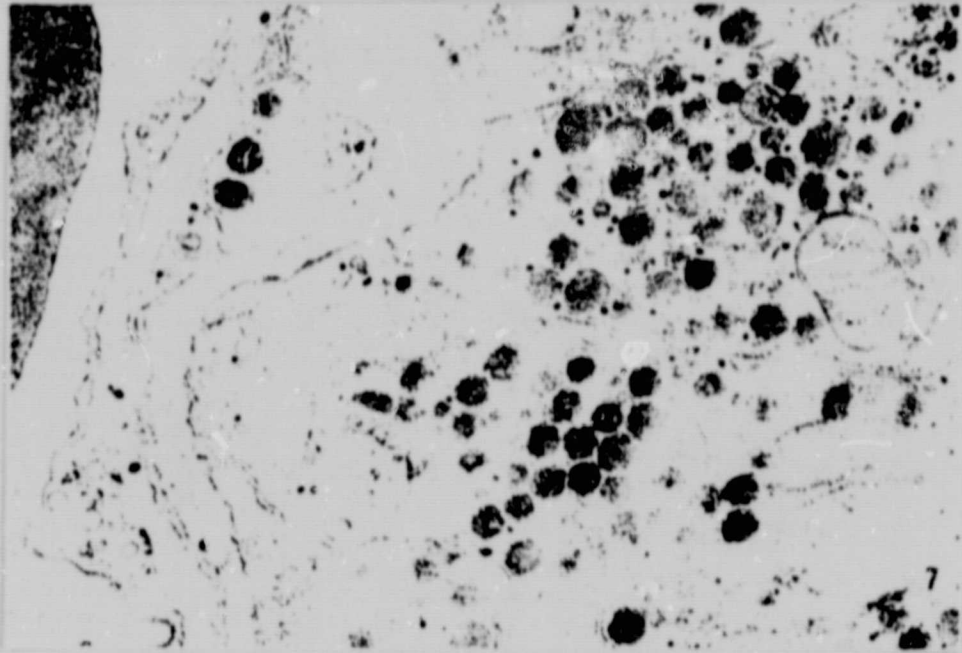


Fig. 7. Two-day complete immobilization. Neurohypophysis. Nerve fibers near blood vessel. Neurosecretory granules, vesicles, mitochondria. X 28,800.

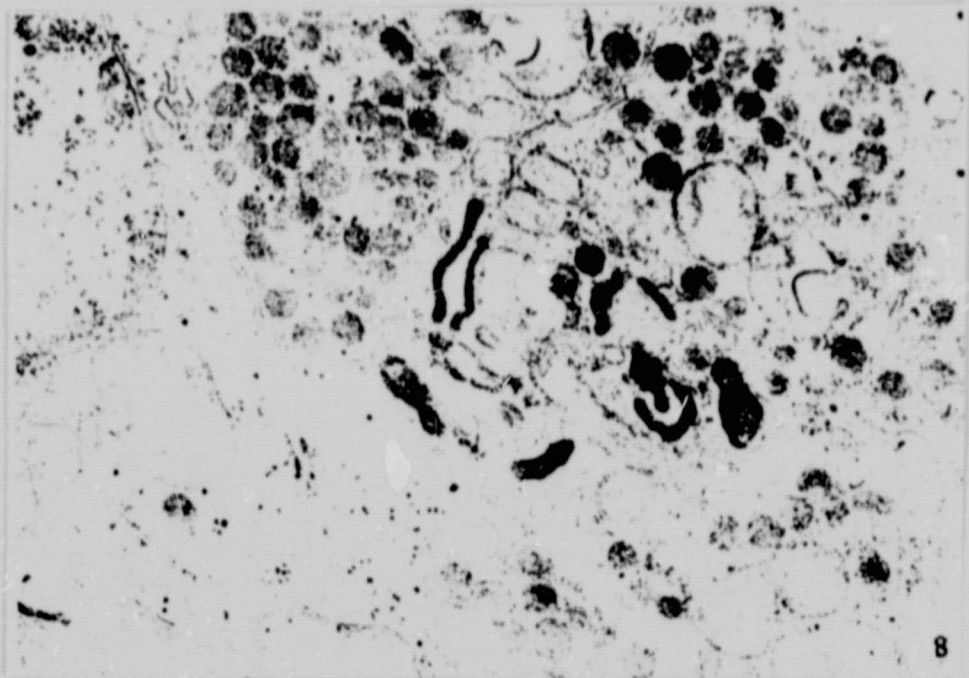
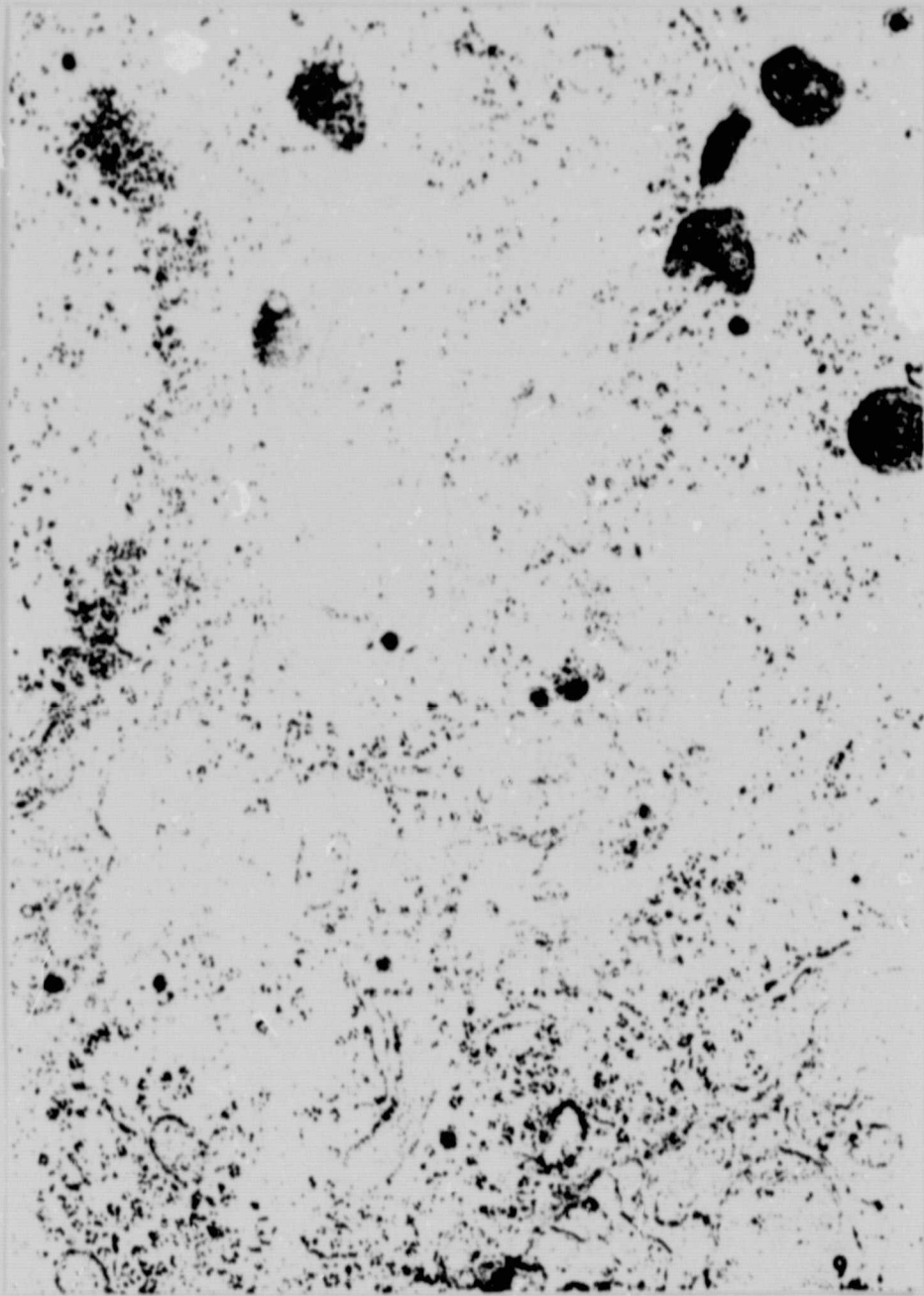


Fig. 8. Two-day complete immobilization. Neurohypophysis. In some fibers myelin figures beside neurosecretory granules and mitochondria. X 28,800.



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Fig. 9. Three-week partial immobilization. Paraventricular nucleus. In a fragment of a neuron numerous dense bodies, lysosomes and single neurosecretory granules. X 28,800.

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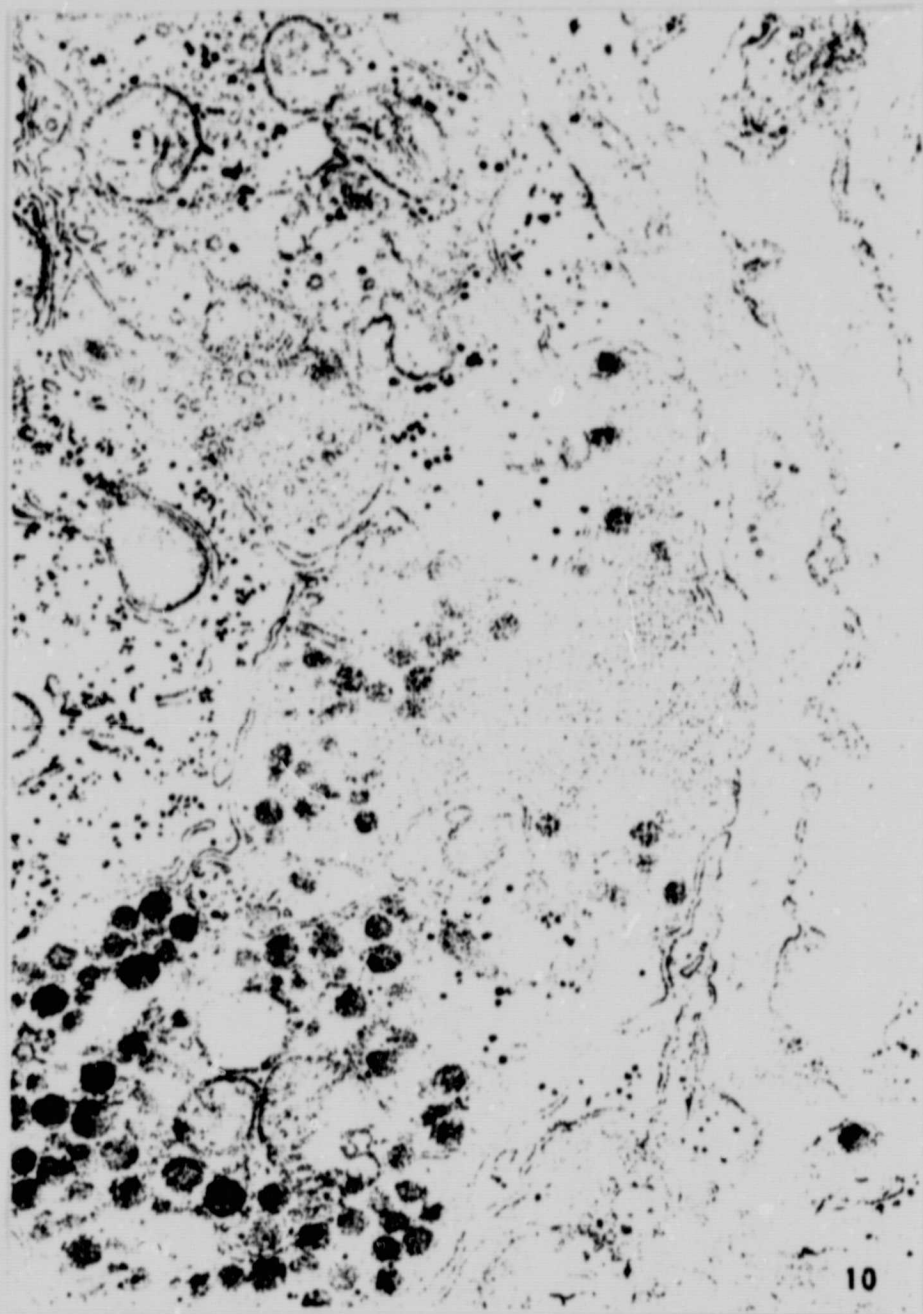


Fig. 10. Three-week partial immobilization. Neurohypophysis. Numerous microvesicles and a small number of neurosecretory granules in fibers adjacent to blood vessels. X 28,800.

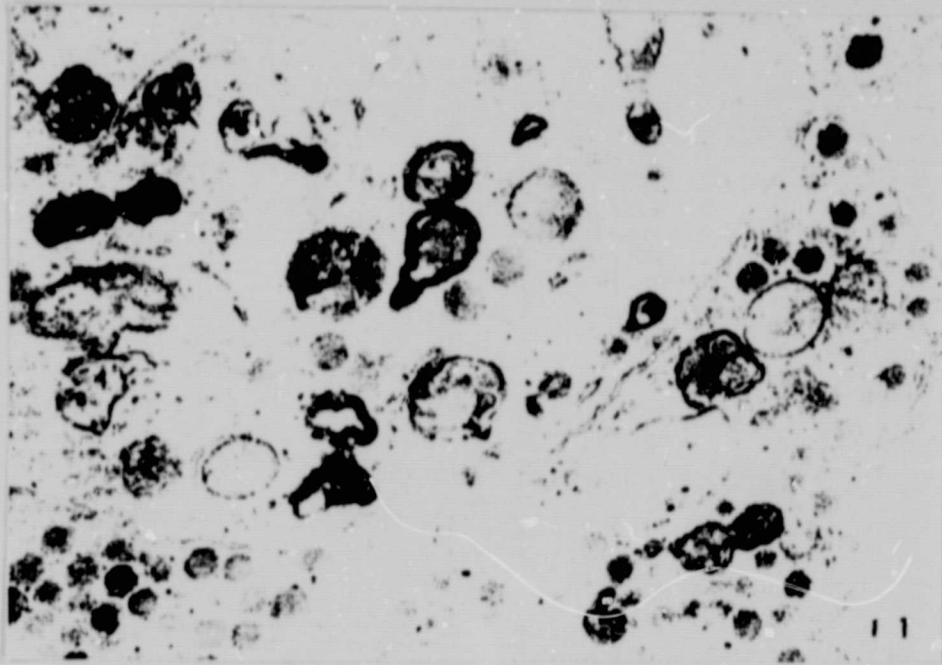


Fig. 11. Three-week partial immobilization. Neurohypophysis. Transverse section. Fibers with numerous myelin figures and small number of neurosecretory granules, neurotubules. X 28,800.

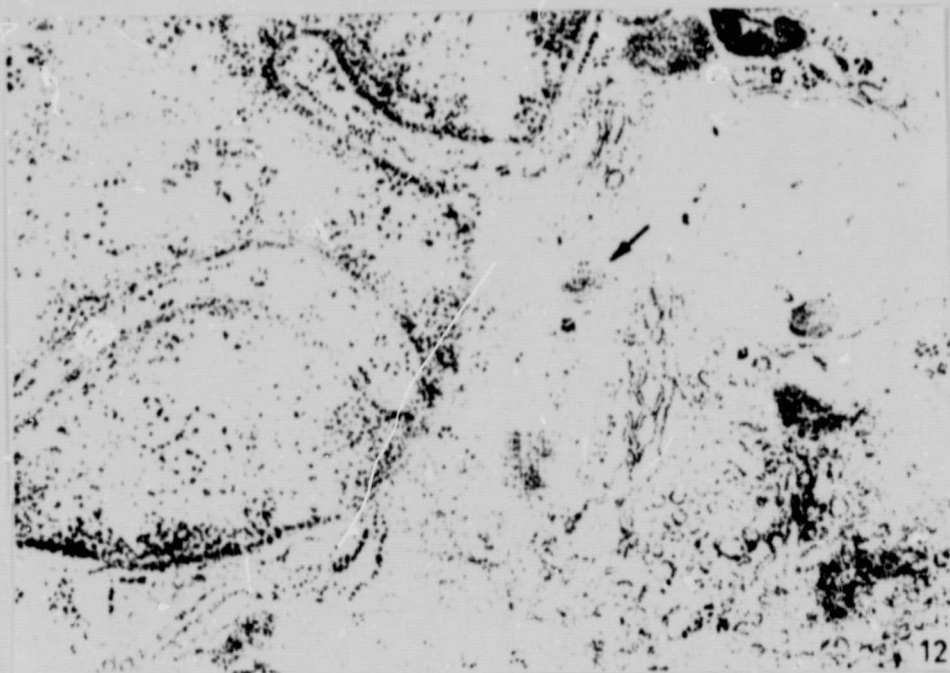


Fig. 12. Three-week partial immobilization. Neurohypophysis. Fragment of pituicyte with large, irregularly shaped nucleus. In cytoplasm well developed Golgi apparatus and granules resembling neurosecretory granules (arrow). X 28,800.

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lamo-hypophyseal system we observe a large amount of neurosecretory granulation that is typical, enveloped by a single membrane and full of a homogeneous substance of great electron density. Beside these granules there are still others, likewise enclosed in membrane but filled with a material that is fine grained and shows less electron density, and a third type of granules with an imperceptible enveloping membrane (Fig. 5). In the fibers we find a variable amount of mitochondria and very many neurotubules, perfectly visible in the profiles of the elongated fibers (Fig. 6). Fibers lying adjacent to blood vessels have a significant number of microvesicles (Fig. 7). We likewise encounter fibers which, aside from the structures mentioned above, contain a large number of lysosome-like bodies and membranous bodies (Fig. 8). In the pituicytes one can see a well developed ergastoplasmic reticulum as well as a considerable number of structures of the lipid type that occupy large portions of the cytoplasm.

2. Electron Microscope Study of Animals Subjected to 3 Week Partial Immobilization

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Supraoptical and Paraventricular Nucleus

In this group too the neurons of both neurosecretory nuclei show the same type of morphological changes and therefore we treat them together. Secretory cells close to each other have characteristic cellular nuclei showing only a slight invagination of the nuclear membranes. Nuclear chromatin is evenly distributed and the electron dense nucleole is usually by itself. The GERL complex is located in the circumnuclear region. We find a well developed Golgi apparatus around which there is a predominance of minute vesicles and multivesicular bodies. Neurosecretory granules occur only individually, but one is struck by the large number of lysosomes, dense bodies or lysosome-like formations with droplike clear intervals (Fig.9). (Fig. 9). The ergastoplasmic reticulum is very highly developed, particularly in the peripheral portions of the neuron and regularly covered with ribosomes, while in the cytoplasm we find a large number of polyribosomes. Mitochondria appearing in the region of the

Golgi apparatus are usually oval or elongated, with a dense matrix. The number of neurotubules scattered at random in the cytoplasm is decidedly less than in the group described previously. In the cytoplasm we encounter likewise loosely arranged nucleoid bodies, as they are called.

Neural Portion of the Hypophysis

The nerve fiber endings contain less neurosecretory granules as compared with the experimental group described above. Besides granulation we encounter there spherical mitochondria, microvesicles and neurotubules as well as individual glycogenous granulations. In the fibers located next to blood vessels there appears to be an increase in the number of microvesicles (Fig. 10). Among the fibers that are nearly normal in structure we likewise find single fibers containing many lysosomes and myelin figures that occur side by side with the neurosecretory granules, single mitochondria and rather numerous neurotubules (Fig. 11). However, the pituicytes encountered are marked by the presence of a large nucleus, frequently irregular in shape, and they boast a highly developed Golgi apparatus. In their cytoplasm we find a rather large number of fatty bodies and at times granulation reminiscent in its structure of the neurosecretory type (Fig. 12). /429

Discussion

On the basis of the results presented we may affirm, that under conditions where a stress factor is active, as was the case in our experiment with immobilized animals, there is stimulation of the hypothalamo-hypophyseal system. The reaction by the system under study -- the production and release of an antidiuretic hormone or of other hormones, depending upon the type of stress factor used -- is hard to assess when one uses only morphological methods. On the basis of observed changes only an indirect judgment may be made about the activation of the secretory neurons being studied, which is accompanied by the production and release of hypothalamic hormones. Until now it has been thought that the supraoptic nucleus

is responsible for the production of the antidiuretic hormone and that the paraventricular nucleus produces oxytocine (Thorn, 1970), whereas on the basis of other reports (Tasso et al., 1976) we might conclude that vasopressin and oxytocine are produced both in the supraoptical and paraventricular nucleus but in separate neurons. Without respect to the type of hormone, it appears that these hormones as well as their transport proteins -- neurophysines -- are synthesized in the neurosecretory centers and transferred to the neural lobe of the hypophysis, evidence of which fact may be the grouping of neurosecretory granules in the vicinity of the presynaptic membrane (Green, 1966). The protein nature of the hormones produced by the secretory cells permits us to suppose that the current state of protein synthesis may attest to the condition of the neuron's activity. The rate and intensity of this synthesis may be an index of the active condition of the neurosecretory system. We may form an idea of the state of protein synthesis in the cell on the basis of morphological studies using the electron microscope, assessing the retention of ultrastructures associated with such synthesis (cellular nucleus, GERL complex, ergastoplasm), on the basis of histochemical studies of enzymes that are markers of individual structures, and also on the basis of autoradiographic examination. By comparing the time needed to incorporate an amino acid radioisotope into the neurons of the supraoptical and paraventricular nucleus, we may judge the rate of protein synthesis and thus of neurosecretion. The advantage of such research is that it makes possible observation of the transfer of labeled material from the synthesis site to the neural portion of the hypophysis (Kwarecki, 1973; Heap et al., 1975).

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Numerous studies have been made on the stimulation or inhibition of protein synthesis in the hypothalamo-hypophyseal system. The stressogenic factors used may be divided into three groups:

- I hormonal
- II chemical antimetabolites
- III physical factors.

Research of an experimental kind on the factors belonging to the first group usually deals with the antidiuretic hormone, CRF, hypophyseal hormones and the suprarenal cortex (Stark et al., 1974; Lymangrover, Brodish, 1974; Gajkowska, 1975, 1976; Danielewicz, 1975). The frequently used chemical antimetabolites include: morphine, alcohol, actinomycin D, colchicin, cycloheximide, vinblastine, etc. (Boudier, 1973; Santolaya, Echandia, 1975; Gajkowska, Borowicz, 1966; Borowicz et al., 1977). Use has also been made of physical factors such as: increased temperature, dehydration induced by refusing water or by giving NaCl, starvation, cutting the peduncle of the infundibulum and other methods used to immobilize animals (Borowicz, Gajowska, 1972; Norström, Sjöstrand, 1972; Vladimirov, Ivanova, 1976).

In our experiment all observed changes in the ultrastructure of the neurons of the supraoptic nucleus, paraventricular nucleus and neural portion of the hypophysis indicate stimulation of the neurosecretory system for the animals totally immobilized for two days. Changes testifying to intensive protein synthesis, which is always preceded by m-RNA synthesis, are observed already in the ultrastructure of the cellular nucleus of the secretory neurons studied. The nucleole shows a pronounced increase in volume, although in the nucleoplasm in the vicinity of chromatin fibers we can see many perichromatin granules, which probably under these stress conditions play a role in the transport of preribosomal RNA from the nucleus to the cytoplasm (Gajkowska, Puvion, 1977). Evident changes likewise indicate the presence of the GERL complex. The canals of the Golgi apparatus are greatly enlarged and at times we see in them material of average electron density which undergoes separation from the smooth membranes of the Golgi apparatus and retains its laminar covering that is probably derived from these membranes. In its vicinity we see a large number of minute vesicles reminiscent of immature neurosecretions and finally numerous neurosecretory granules as well as multivesicular bodies. Such pictures have been described in other experimental systems by many authors and interpreted as a sign of the activity of neurons (Flamand-Durand, Dustin, 1972; Borowicz, Gajkowska, 1972; Gajkowska, 1975).

Chance does not seem to be at the bottom of the appearance of the numerous neurotubules, whose role and importance has been widely discussed in recent years.

It is hypothesized that they play a role in various phenomena of the cellular cycle which are associated with cytoplasm movement (Rebhun, 1972) or with the intracellular movement of organelles and other cellular inclusions. The most recent studies of Grainger and Sloper (1971) have shown, that in the hypothalamo-hypophyseal system they are responsible for the transport of polypeptides. This is also borne out by our findings, since the considerable increase in the number of neurotubules in neuron bodies, as we found out, and likewise along the whole course of neural fibers and even at their extremities is evidence of an intensified rate in the flow of neurosecretory granules to the neural portion of the hypophysis.

We also find interesting the presence, in the cytoplasm of the neurons studied, of nucleoid bodies. On the basis of a fairly abundant literature already existing on this subject one may assert that they appear and always under conditions where the neurons in question are stimulated (castration, dehydration, adrenalectomy). Their exact provenience and significance physiologically is still quite controversial. The recent research (Hindelang-Gertner et al., 1974) suggests that they are composed of ribonucleoprotein and have a nuclear origin. 437 Since they are found not only in cellular cytoplasm but likewise in the axons, we may presume that they represent preribosomal material.

In the group of animals whose locomotive ability was limited for three weeks we observed changes less severe and of a slightly different type in the ultrastructure of the neurons studied in the supraoptic and paraventricular nucleus and in the neural lobe of the hypophysis.

On the basis of the ultrastructural changes established (growth of nucleus and nucleole, well developed Golgi apparatus but in this system forming dense bodies and lysosomes rather than neurosecretory granules, i. e. creating its own aspect of "maturation" (Picard et al., 1972), we must assume that in the initial stage of this incomplete im-

mobilization the hypothalamo-hypophyseal system might react through changes similar to those established for animals subjected to short-term total immobility but that prolonged stress induced by the restricted state of animal movements might create the possibility of adaptation to altered conditions by the organism. The presence of numerous lisosomal structures both in the neuron bodies and in the fibers of the hypophyseal neural lobe is possible associated with the regulation of excessive secretory granulation (Boudier, Picard, 1976) synthesized, as we suppose, in the first stage of stress.

We must emphasize the fact that only a small amount of neurotubules appeared in the neurons of both secretory nuclei in this experimental group and only a small number of microtubules in the fibers of the neural portion of the hypophysis. Relying on recent reports in the literature we are able to form an opinion on the reduced rate of neurosecretory granule flow from the hypothalamic neurons to the neural portion of the hypophysis in those animals who were subjected to partial immobilization for three weeks.

Conclusions

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Stress due to animal immobilization induces stimulation of the hypothalamo-hypophyseal system in the rat.

1. Total immobility for two days produces these effects in the neurons of the suproptical and paraventricular nucleus:

- augmented production of neurosecretory granulation manifested morphologically by:

- a) growth of nucleus and nucleole,
- b) highly developed ergastoplasmic reticulum,
- c) highly developed Golgi apparatus,
- d) large amount of neurosecretory granules.

- acceleration of neurosecretory granule transport from neuron bodies to their extremities in the neural portion of the hypophysis, manifested morphologically by the increase in neurotubules.

- increased buildup of neurosecretory granulation in the endings of the fibers in the neural portion of the hypophysis, morphologically

matched perhaps by the occurrence of granulation with different electron density and a large number of microvesicles in fibers close to blood vessels.

2. Changes of a different type and lower intensity appear in animals subjected to three weeks partial immobilization and this may be an expression of how this system, as well as the whole organism, adapts to varying conditions.

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