ROLE OF THE SYMPATHETIC NERVOUS SYSTEM IN THE PATHOGENESIS OF RETINAL DEGENERATION IN ONTOGENY

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After desympathization of mice with the aid of antiserum against growth factor of the sympathetic nervous system, the increase in the RNA and protein concentration in the retina is inhibited and ATPase activity in the neurons is reduced. Degeneration of the retina is characterized by vacuolation of the outer segments of the photoreceptors, dilatation of the cisterns of the Golgi apparatus of the inner segments, and destruction of the cristae of the mitochondria chiefly in neurons of the ganglionic layer.

KEY WORDS: desympathization; ontogeny; degeneration of the retina.

The influence of the sympathetic nervous system on nutrition of the retina has been established [1, 5, 7, 12]. However, the mechanism of development of degeneration after disturbance of the innervation of the retina is not clear.

To study the mechanism of development of retinal degeneration after desympathization during ontogeny in mice the content and distribution of DNA, RNA, protein, and ATPase activity were investigated as components closely linked with visual function and playing an important role in the processes of formation of the organ [3, 4, 8].

EXPERIMENTAL METHOD

Desympathization was carried out with antiserum (Wellcome, England) against growth factor of the sympathetic nervous system. The serum was injected into 20 BALB mice for 5 days in a dose of 500 units/g body weight. The animals were killed 1 and 2 weeks and 1 and 3 months after the beginning of the experiment. The eye was fixed in Carnoy's fluid for the investigation of DNA, RNA by Bracket's method, and proteins after staining with Amido Black 10B. After fixation of the material in 10% neutral formalin solution, ATPase activity was determined [11]. Material for electron microscopy was stained with uranyl acetate and lead citrate.

EXPERIMENTAL RESULTS

In the control animals at the age of 1 week all layers in the central zones of the retina were formed. Only the outer segments of the photoreceptors were incompletely differentiated and the outer plexiform layer ill defined. In the peripheral zones of the retina no clear line of demarcation could be seen between the cells of the outer and inner nuclear layers. The outer segments of the photoreceptors were virtually unformed and the inner segments poorly differentiated. The nuclei of the ganglionic cells had a delicate

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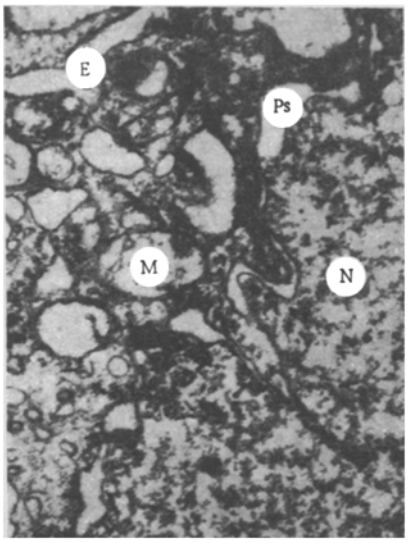

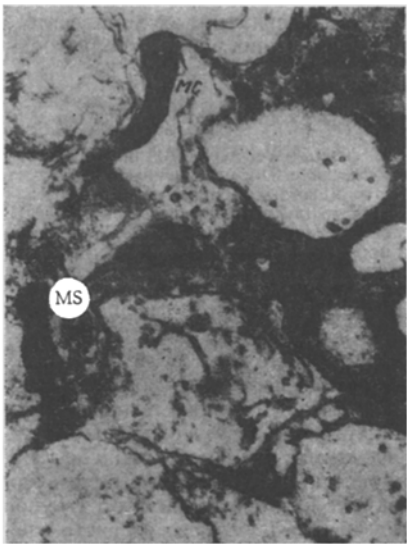

Fig. 1 Fig. 2

Fig. 1. Retinal ganglionic cell of a desympathized mouse: N) nucleus; M) mitochondria; Ps) perinuclear space; E) endoplasmic reticulum, 15,000×.

Fig. 2. Myelin-like structures (MS) in axons of ganglionic cells of a desympathized mouse, 13,400×.

chromatin structure. The chromatin structure in the neurons of the inner and, in particular, the outer nuclear layer was coarser than in the ganglionic cells.

The DNA concentration fell from the outer nuclear layer toward the layer of ganglionic cells. DNA was present in the structure of the chromatin both in the nuclei of the ganglionic cells and in neurons of the outer and inner nuclear layers.

The decrease in the RNA concentration from the layer of ganglionic cells toward the layer of photoreceptors could be clearly traced. Proteins in the retina of animals of this age can be detected in practically all formed structural elements. In the actively formed plexiform layers and segments of the photoreceptors the protein concentration was a little higher than in the adult animal. ATPase activity was more marked in the blood vessels than in the nerve cells and fiber structures of the retina. In the latter, the enzyme activity was highest in the ganglionic cells, then in the neurons of the inner and outer nuclear layers and, finally, in the plexiform layers.

In animals aged 2 weeks, as differentiation of neurons of the inner and outer nuclear layers took place there was some decrease in the DNA concentration in the nuclei and an increase in the RNA concentration gradient in the cell cytoplasm. The formation of the layer of rods was accompanied by a higher concentration of RNA and protein in the latter than in the perinuclear cytoplasm of the photoreceptors.

In animals aged 1 month the process of structural and chemical differentiation of the retina could be regarded as essentially complete. The ganglionic cells had the heterogeneity of structure characteristic of the cells of each type, with a variable character of distribution of RNA, protein, and ATPase activity. The variability of distribution of these substances was less marked in the inner nuclear layer than in the ganglionic cells. A more or less equal distribution and content of RNA, protein, and ATPase activity were observed in the photoreceptor cells, with a higher concentration of these substances in the inner segments than in the outer segments. The protein concentration in the plexiform layers was lower than in animals of the younger age groups.

In the animals aged 3 months the structure of the retina did not differ significantly from that in the mice aged 1 month. Histochemically, some decrease in the concentration of RNA and proteins could be seen in the retina compared with animals aged 1 month.

In desympathized animals aged 1 week the structural and chemical differentiation of the retina was delayed. This was shown by a slower than normal increase in the RNA concentration gradient and late differentiation of the neurons of the outer and inner nuclear layers. The protein concentration and ATPase activity were below normal.

In the animals aged 2 weeks the delay in the structural and chemical differentiation, as shown by the RNA concentration gradient, was less than in the animals aged 1 week. By contrast, in the highly differentiated ganglionic cells changes in the shape of the cells were observed, with displacement of the nucleus toward one pole and of the Nissl's substance toward the other pole of the cell.

In the animals aged 1 month no significant changes in the RNA and protein concentration or the ATPase activity in the neurons of the outer and inner nuclear layers could be seen compared with those aged 2 weeks. The deformation and reduced density of the ganglionic cells were clearly visible, especially in the small and middle-sized cells; this was accompanied by a decrease in the concentration of the substances studied.

Electron-microscopic examination of the retina of a desympathized mouse aged 1 month showed features of degeneration in all the neurons. The greatest changes were found in the ganglionic cells: more marked destruction of the cristae of the mitochondria (Fig. 1). Growth of the components of the smooth endoplasmic reticulum and dilatation of the cisterns of the Golgi apparatus, with an increase in the number of lysosomes and the appearance of myelin-like structures, were characteristic (Fig. 2). Together with cells of normal structure, cells with vacuolation of the outer segments and some disorganization of the lamellar structures could be seen in the photoreceptors. In the inner segments the cisterns of the Golgi apparatus were dilated, the matrix was translucent, and the cristae in the mitochondria had disappeared. In the cells of the inner nuclear layer the perinuclear spaces were widened and the nuclei pycnotic.

In the animals aged 3 months the degenerative changes described above in the retina were more marked and were accompanied by a substantial decrease in the RNA and protein concentrations compared with the animals aged 1 month.

These data on changes in the RNA concentration gradient during development of the retina indicate that under normal conditions structural and chemical differentiation is complete in the ganglionic cells sooner than in neurons of the outer and inner nuclear layers. After desympathization, the increase in the concentration gradient of RNA in neurons of the outer and inner nuclear layers is delayed, indicating a decrease in morphogenetic activity. However, in the mice aged 1 month there was hardly any difference between the control and experimental series. Desympathization evidently does not act powerfully enough to change the genetically determined regulation of morphogenetic activity [2, 9].

Degenerative changes in the ganglionic cells of desympathized mice at the ages of 1 and 3 months are possibly connected with the higher rate of protein metabolism in these cells, as autoradiographic studies have shown [10]. The predominance of degenerative changes in the ganglionic cells have also been revealed by administration of chlorpromazine [6], a drug with sympatholytic action.

These investigations show that the sympathetic nervous system participates in the regulation of the nucleoprotein metabolism of the retina. Desympathization disturbs nutrition mainly in the ganglionic cells, as the elements with the highest level of nucleoprotein metabolism.

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