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MORPHOLOGICAL SIGNS OF REGENERATION AND HYPERTROPHY OF BRAIN NEURONS

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Abstract

Objective. Generalization and systematization of literature data on regeneration and hypertrophy of brain neurons.

Methods. The basis of this study was a review of the literature on this topic.

Results. There are several ways to regenerate neurons: intracellular regeneration, restoration of the neuropil, the formation of new neurons (in some parts of the nervous system – the hippocampus, the subventricular layer of the lateral ventricles and olfactory bulbs) and the formation of heterokaryons (fusion of a neuron with an oligodendrocyte). Hypertrophy of neurons may indicate both compensation and the development of a pathological process. To clarify the nature of this phenomenon, it is necessary to conduct an ultramicroscopic study of the organelles of the nerve cell.

Conclusions. The subsequent study and detailing of the processes of regeneration and hypertrophy of neurons, especially of the central nervous system, will significantly improve the quality of prevention, diagnosis and treatment of neurodegenerative diseases.

Keywords: neurons, brain, regeneration, hypertrophy

МОРФОЛОГИЧЕСКИЕ ПРИЗНАКИ РЕГЕНЕРАЦИИ И ГИПЕРТРОФИИ НЕЙРОНОВ ГОЛОВНОГО МОЗГА

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Резюме

Цель. Обобщение и систематизация данных литературы о регенерации и гипертрофии нейронов головного мозга.

Методика. Основой данного исследования стал обзор литературы по данной теме.

Результаты. Существует несколько способов регенерации нейронов: внутриклеточная регенерация, восстановление нейропиля, образование новых нейронов (в некоторых отделах нервной системы – гиппокампе, субвентрикулярном слое боковых желудочков и обонятельных луковицах) и образование гетерокарионов (слияние нейрона с олигодендроцитом). Гипертрофия нейронов может свидетельствовать как о компенсации, так и развитии патологического процесса. Для уточнения характера данного явления необходимо проведения ультрамикроскопического изучения органелл нервной клетки.

Заключение. Последующее изучение и детализация процессов регенерации и гипертрофии нейронов, особенно, центральной нервной системы, позволит значительно повысить качество профилактики, диагностики и лечения нейроденеративных заболеваний.

Ключевые слова: нейроны, головной мозг, регенерация, гипертрофия

Introduction

The brain and the nervous system as a whole are frequent objects of experimental study. As a rule, in the course of a scientific study, the reaction of neurons to the effect of a damaging factor or the effectiveness of the corrective effect of pharmacological drugs is assessed. In this regard, when modeling the

experimental pathology of the nervous system, the criteria for regeneration and hypertrophy of neurons are important [3, 8]. Regeneration is an adaptive reaction of the nervous system, manifested by the neoplasm of structural elements of neurons instead of dead ones, while hypertrophy means an increase in the size of perikaryons and an increase in the number of organelles, leading to an increase in the functional activity of the cell [9]. The purpose of this article is to systematize information about the morphological signs of regeneration and hypertrophy of brain neurons.

Regenerative changes

Speaking about the regeneration of neurons, they usually mean the restoration of damaged processes of nerve cells, that is, the regeneration of nerve fibers and synapses. In the course of many years of morphological studies, it was found that the regenerative process in neurons is manifested by the restoration of damaged and the formation of new processes of the neuropil, as well as the appearance of additional collaterals on the existing processes. Neuropil neoplasms lead, in turn, to a complication of the structure of neuronal dendrites. These changes can occur not only in neurons with damaged processes, but also in normal neurons, with the death of other nerve cells [8, 9].

Most often, regenerative rearrangement is detected in the extra- and intramural ganglia of the intervertebral and cranial sensory nodes. This may be due to the fact that the neurons of the sensory ganglia have only one T-shaped process [15]. Therefore, in the case of the appearance of regenerative changes in them, it is easier to detect new branches of the neuropil, often having a spiral shape with distal thickenings (microneuromas). Thus, if part of the neurons of one or another part of the nervous system die, then a regenerative process takes place in the remaining neurons, accompanied by hyperplasia of the neuropil and subsequent hypertrophy of the cell body itself [39]. The degree of restoration of the function of the nervous system is determined not only by the volume and nature of its damage, but also by the localization of the process, since the plastic capabilities of neurons in different parts of the central and peripheral nervous system are far from the same [20, 22].

So, in the central nervous system, the regeneration of the neuropil is slower and does not always complete successfully. At the same time, peripheral nerve fibers regenerate relatively well. The process, as a rule, begins with the formation of retraction balls on the proximal segments of the axons, with clavate influxes of neuroplasm, which then disappear [11]. Normal regeneration of the neuropil is always accompanied by proliferation and hypertrophy of oligodendrocytes, which form the cords that guide axonal growth [22]. Sometimes, during the growth of an axon, flask-like thickenings appear at its end, which indicates a violation of the normal course of regeneration, especially if new branches lose their connection with oligodendrocytes. This phenomenon is usually observed when there is an obstacle in the path of the growing neuropil [12, 39].

Regenerating axons first grow along the strands of oligodendrocytes, and then they are enveloped in folds of their cytolemma, which forms mesaxons. At the first stages of regeneration, part of the strands of oligodendrocytes may include several axons. However, in the future, only one is preserved and covered with myelin, the rest disappear [9]. Regeneration is considered complete when the axon reaches the original innervated tissue and forms a synapse with the working organ [11,20]. In the morphological study of histological specimens, it is sometimes difficult to distinguish between a normal nerve ending (the result of successful regeneration of the neuropil) from pathological branching with microneurium proliferation [13]. The differences lie in the fact that microneuromas usually do not have a capsule and consist of randomly intertwining thin myelin-free nerve endings. These data indicate that neurons have rather high regenerative capabilities [20]. The restoration of the structure of the nervous tissue after its damage in most departments is carried out not through the division of the preserved neurons, but due to the regeneration and hyperplasia of their neuropil, which leads not only to the restoration of the lost, but also to the establishment of new connections between the nerve cells and the innervated organ. In some cases, the regeneration of nerve fibers and end apparatus is disturbed and accompanied by the formation of neuromatous growths, which may be the cause of the appearance of pathological reflexes [12, 13, 15, 22, 39].

However, there are data in the literature on the division of neurons in the central nervous system of adult mammals and humans [37]. In 1998, the fact of postnatal neurogenesis in the human hippocampus was established using the molecular marker bromodioxyuridine (BrdU) [26]. In addition, new neurons were integrated into the general neuropil network [21, 27, 29, 32, 36].

Also, postnatal neurogenesis was noted in the subventricular layer of the lateral ventricles and olfactory bulbs [3, 31, 34]. However, the presence of the formation of new neurons in adult mammals and humans remains controversial [3, 25, 30, 31, 35].

However, the process of studying neurogenesis is complicated and can give false results, since BrdU can also be turned on during reparative DNA synthesis in a neuron after its damage and can cause an

erroneous determination of the fact of neuron division. It is believed that one of the forms of regeneration is the formation of nerve cell heterocarins. They are described in an electron microscopic level. In these structures, the fusion of the nuclei of neurons and oligodendrocytes was observed [3, 7, 28].

Gradually, in the heterokaryon, the nucleus of the oligodendrocyte is reprogrammed and it gradually becomes more and more similar to the nucleus of the neuron in size, shape, structure of chromatin [3, 4]. Upon completion of the reprogramming process, the kernels become indistinguishable. [10] Heterokaryon turns into a cell with two identical nuclei – dikarion [4, 7]. Thus, as a result of fusion and reprogramming, a second nucleus is formed in the neuron, and the functionality of the neuron increases significantly. This is important to compensate for the loss of a certain number of neurons during damage. The presence of such dicarions has been described in the cerebral cortex in the area adjacent to the focus of postischemic necrosis [3-5, 7, 10, 28, 31, 35].

Hypertrophic changes in neurons

Hypertrophy of neurons is observed most often due to either the death of a part of the nerve cells, while the remaining neurons take over their function and hypertrophy, or by the enhanced work of this part of the nervous system [1, 2, 18, 19]. Thus, neuronal hypertrophy can occur both on a pathological and physiological basis. As a rule, hypertrophic changes in the structures of nervous tissue are not always compensatory, since the functional concept of "compensation" is broader than the morphological concept of "hypertrophy". Hypertrophy of neurons is manifested mainly by an increase in the size of the perikarion, nucleus and nucleolus [38]. There may be neurons with two or more nucleoli (Fig. 10).

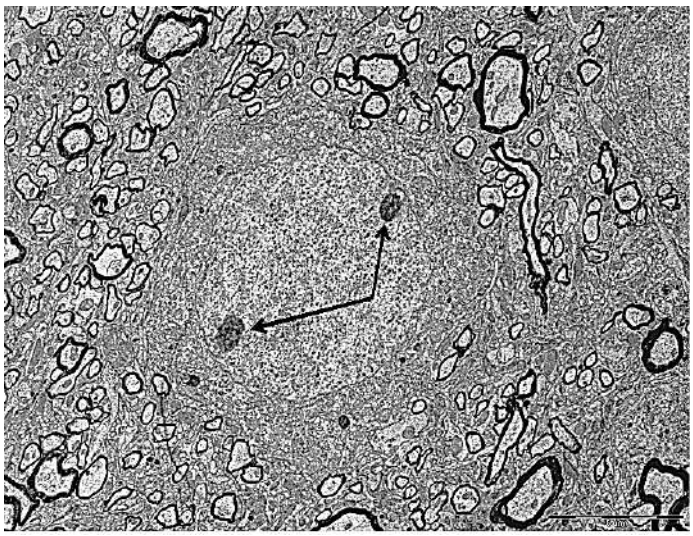

Fig. 10. Neuron of the inner pyramidal layer of the parietal cortex of the brain of an adult rat. Fragment of the cytoplasm. The nucleus has two nucleoli (indicated by arrows). Digital micrograph. Electron microscopy. Magnification: 25000. Scale bar: 5 microns

An increase in the number and enlargement of lumps of chromatophilic substance is observed, that is, an increase in the length of the cisterns of the granular endoplasmic reticulum and the number of ribosomes associated with it, hyperplasia of neurofibrils, thickening of the neuropil [1,2]. At the same time, the axons thicken somewhat and sometimes contain varicose enlargements along their course. However, an increase in the size of perikaryon neurons in itself cannot be a sign of hypertrophy, as it is often observed in dystrophic processes [6]. To differentiate between these phenomena allows electron microscopic study of organelles. With neuronal dystrophy, destruction of the endoplasmic reticulum is noted, the loss of ribosomes by it, disorganization of the Golgi complex, swelling and destruction of cristae in mitochondria. At the same time, hypertrophied neurons carrying an increased load are functionally depleted over time and undergo dystrophic, necrobiotic and necrotic changes [23]. One of the manifestations of neuronal hypertrophy is intense staining of their cytoplasm according to the Nissl method (hyperchromia) [24]. According to the shape of the perikarion, hyperchromic neurons are subdivided into non-shrunken and shrunken. Under normal conditions, in the brain of animals and humans, there are only single “dark” hyperchromic and hyperchromic shrunken neurons. Their number can increase significantly under experimental influences and pathological conditions [23].

Popova E.N. isolated 3 types of hyperchromic neurons in the cerebral cortex of rats at the electron microscopic level [6]. Hyperchromic cells of the first type contain a nucleus that is less osmiophilic in comparison with the cytoplasm, and the cytoplasm contains expanded cisterns of the endoplasmic reticulum, disintegrated into vacuoles of the cisterns of the Golgi complex, mitochondria with destroyed cristae [2]. In hyperchromic cells of the second type, the osmiophilia of the cytoplasm is markedly increased due to the accumulation of fine-granular material, and the compacted nucleus acquires irregular outlines. Hyperchromic neurons of the third type have a dark, irregularly shaped nucleus. In their densified cytoplasm, slit-like seals and damaged organelles are revealed [6]. Hyperchromatophilia of neurons can characterize the predominance of protein synthesis over its consumption, and shrinkage with dehydration of the cytoplasm, possibly, occurs in connection with a violation of the water-salt metabolism of neurons. According to our data, hyperchromic neurons had much more connected and, especially, free ribosomes, which ensures their hyperchromic Nissl staining [1, 40] (Fig. 2, 3).

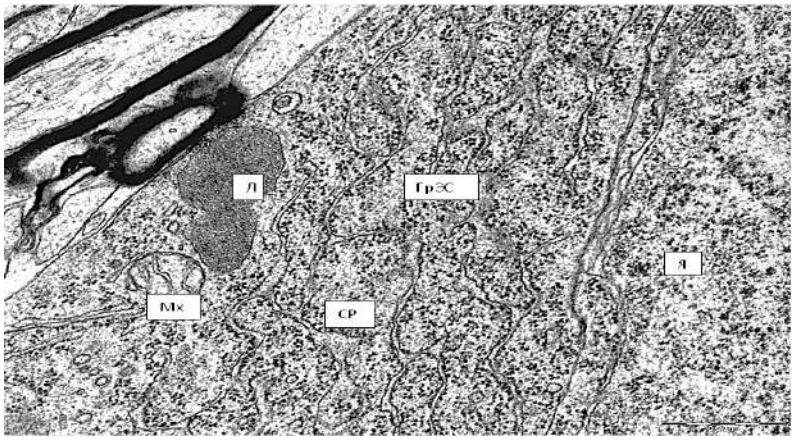

Fig. 2. Hyperchromic non-wrinkled neuron of the inner pyramidal layer of the parietal cortex of an adult rat. Fragment of the cytoplasm. Digital micrograph. Electron microscopy: nucleus (Я), mitochondria (Мх), lysosome (Л), free ribosomes (СР), ГрЭС – granular endoplasmic reticulum. Magnification: 50,000. Scale segment: 0.5 microns

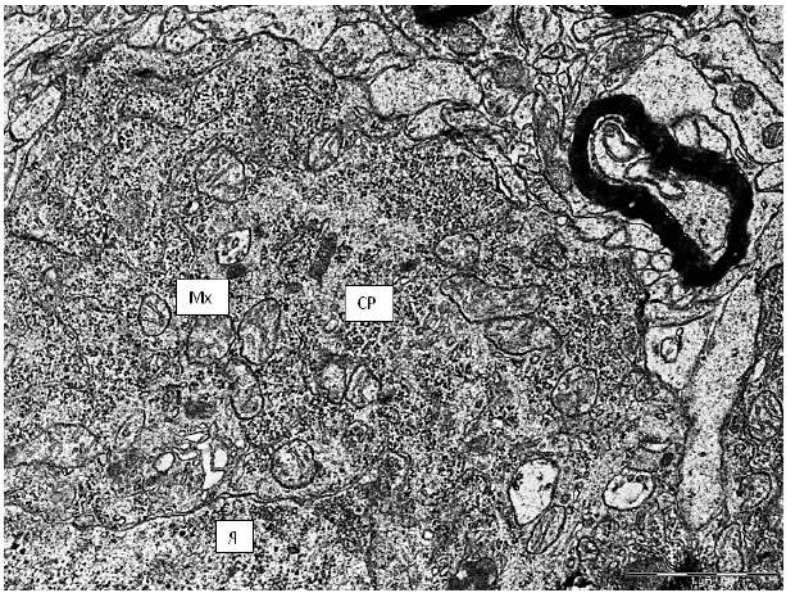

Fig. 3. Hyperchromic non-wrinkled neuron of the inner pyramidal layer of the parietal cortex of an adult rat. Fragment of the cytoplasm. Digital micrograph. Electron microscopy: nucleus (N), mitochondria (Mx), free ribosomes (CP). Magnification: 50,000. Scale segment: 0.5 microns

A decrease in the number of ribosomes associated with the granular endoplasmic reticulum and an increase in the number of free ribosomes indicates that protein biosynthesis is switched for the neurons' own needs, which is necessary for their survival in unfavorable conditions [40]. However, due to reduced protein synthesis for export and its transport to the terminals, the participation of these neurons in the activity of the cerebral cortex is likely to be reduced. Shrinking of a part of hyperchromic neurons can probably be considered as a breakdown in adaptation, leading to their subsequent death [23, 24, 33].

Gallyas put forward a number of ideas that the nature of "dark" neurons is associated with dysfunction of the phase change in the hyaloplasm, capable of restoring normal functioning, and in case of death they are phagocytosed by microglia [16-19].

Conclusion

Thus, there are several ways to regenerate neurons: intracellular regeneration, restoration of the neuropil, the formation of new neurons (in some parts of the nervous system – the hippocampus, the subventricular layer of the lateral ventricles and olfactory bulbs) and the formation of heterokaryons (fusion of a neuron with an oligodendrocyte). Hypertrophy of neurons may indicate both compensation and the development of a pathological process. To clarify the nature of this phenomenon, it is necessary to conduct an ultramicroscopic study of the organelles of the nerve cell. The subsequent study and detailing of the processes of regeneration and hypertrophy of neurons, especially of the central nervous system, will significantly improve the quality of prevention, diagnosis and treatment of neurodegenerative diseases.

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