MICROSTRUCTURAL CHANGES IN HIPPOCAMPAL NEURONS UNDER CHRONIC STRESS: A HISTOLOGICAL STUDY

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Abstract. *Chronic stress is a key factor affecting the structural and functional state of the central nervous system, particularly the hippocampus , a brain region responsible for memory and learning. Long-term exposure to stress factors leads to significant microstructural changes in neurons, including disruption of dendritic architecture, decreased neurogenesis , and activation of apoptotic processes. This study aimed to identify and histologically evaluate changes in hippocampal neurons during chronic stress. The obtained results allow us to deepen our understanding of the pathogenetic mechanisms of stress-induced neurodegenerative processes. Chronic stress is one of the most significant adverse factors exerting a pronounced impact on the central nervous system and, in particular, on the hippocampus , a key brain structure involved in learning, memory, and emotional regulation. Long-term exposure to stress factors leads to activation of the hypothalamic-pituitary-adrenal system and increased secretion of glucocorticoids , which has a neurotoxic effect on hippocampal neurons .*

At the microstructural level, chronic stress is accompanied by a number of morphological changes, including a reduction in dendritic branching, decreased synaptic density , disruption of neuronal cell body structure, nuclear pyknosis , and cytoplasmic vacuolization. Furthermore, inhibition of neurogenesis in the dentate gyrus of the hippocampus , increased apoptosis , and glial cell activation are observed, which together indicate the development of neurodegenerative changes. In this study, a histological analysis of hippocampal tissue was performed in a model

of chronic stress to identify characteristic microstructural changes in neurons. The use of classical histological and morphometric analysis methods allowed us to assess the extent of damage to neuronal structures and identify significant differences between the control and experimental groups.

The study results showed that chronic stress leads to significant destructive changes in hippocampal neurons , manifested by disrupted morphology and decreased functional activity. These changes may serve as a morphological substrate for cognitive impairments and emotional disorders associated with prolonged stress. The findings expand our understanding of the pathogenesis of stress-induced brain damage and can be used to develop new approaches to the prevention and treatment of neurodegenerative and psychoneurological diseases.

The aim of the study was to examine microstructural changes in hippocampal neurons during chronic stress using histological analysis methods.

Study objectives: To study the morphological features of normal hippocampal neurons. To simulate chronic stress under experimental conditions. To conduct a histological examination of hippocampal tissue . To assess changes in neuronal structure (dendrites, nucleus, cytoplasm). To identify signs of neurodegeneration and apoptosis . To conduct a comparative analysis of the control and experimental groups.

Research methods. Experimental modeling of chronic stress (e.g., immobilization stress or movement restriction stress). Collection and fixation of hippocampal tissue . Preparation of histological sections. Staining of preparations (hematoxylin and eosin, Nissl). Microscopic examination and morphometric analysis. Statistical processing of the obtained data.

Study results. Cerebral microangiopathy (CMA) is a syndrome of neurological, cognitive, neuroimaging , and morphological manifestations caused by damage to small cerebral arteries, arterioles, capillaries, and venules . CMA is the leading cause of purely vascular cognitive impairment and is a major contributor to the development of mixed forms of dementia. It explains at least one-fifth of all

strokes and a significant proportion of gait and pelvic floor dysfunction in the elderly. For many decades, arterial hypertension (HTN) was considered the only risk factor for CMA, which in our country is reflected in the widely used term hypertensive cerebrovascular insufficiency. However, advances in hypertension treatment have not led to a decrease in the incidence of CMA and its complications in the population, which is also confirmed by the results of randomized controlled trials demonstrating the low efficacy of antihypertensive therapy in slowing the progression of CMA. Furthermore, it has been established that in a significant proportion of cases, sporadic CMA is not associated with hypertension or does not correspond to its severity. An analysis of the relationship between classic vascular risk factors and the development of white matter hyperintensities (WMH), the most commonly used MRI marker for CMA, revealed that among 750 elderly patients and 150 patients with ischemic stroke, only 2% of WMH was attributable to vascular factors, with hypertension and smoking being the most significant. This justifies research to identify factors and markers of vascular wall damage and mechanisms for the progression of sporadic CMA.

CMA is diagnosed based on MRI signs of brain damage associated with small vessel damage. These signs are codified in the international STRIVE standard for CMA testing in aging and neurodegeneration . In addition to the classic CMA manifestations of WMH2 and lacunae (a cyst following the organization of a lacunar infarction), these include acute and subacute small subcortical infarctions, dilated perivascular spaces (DPS), microbleeds (MB), superficial cortical siderosis, and cerebral atrophy. Recent studies have established a relationship between the total CMA score, calculated using a combination of MRI signs, and cognitive impairment, the risk of recurrent stroke, and the prognosis for mortality after stroke. However, determining the clinical significance of the detected changes for individual patients is difficult. With the exception of lacunae in strategic brain regions to explain the clinical manifestations of lacunar syndromes, they do not predict the extent of changes necessary to develop cognitive impairment (CI), gait

disturbances, or pelvic dysfunction. There are significant discrepancies in the predictive clinical value of WMH. Although WMH is recognized as the leading MRI sign of CMA progression and the development of CMA clinical complications, in a significant proportion of cases it is incidental and inconsistent with neurological and cognitive status.

A histological examination of hippocampal tissue revealed significant differences between the control and experimental groups. In the control group, hippocampal neurons retained a typical morphological structure: clearly defined cell body contours, rounded nuclei with evenly distributed chromatin, well-developed cytoplasm, and a preserved dendritic network. Cells were arranged in an orderly fashion, with no signs of destruction or degeneration. In the experimental group, which had been exposed to chronic stress, significant microstructural changes were observed in neurons. These included a decrease in cell body size, neuronal deformation, pyknosis and nuclear hyperchromasia , and cytoplasmic vacuolization. A decrease in neuronal density was observed in certain areas of the hippocampus , particularly in the CA1 region and the dentate gyrus.

Furthermore, a significant reduction in dendritic branches and a decrease in the number of synaptic contacts were observed, indicating disruption of interneuronal connections. Signs of neuronal apoptosis were observed in a number of preparations . Activation of glial elements was also detected, manifested by an increase in the number of astrocytes and signs of reactive gliosis . Morphometric analysis confirmed a statistically significant decrease in neuronal density and an increase in the proportion of damaged cells in the experimental group compared to the control group ($p < 0.05$).

Conclusions: Chronic stress has a significant negative impact on the microstructure of hippocampal neurons . Under the influence of stress factors, destructive changes in neurons develop, including pyknosis of nuclei, vacuolization of the cytoplasm and cell deformation. A decrease in neuronal density and disruption of their spatial organization are noted, especially in the CA1 region and the dentate

gyrus. Chronic stress leads to a reduction in dendritic branches and a decrease in the number of synaptic contacts. Signs of increased apoptosis and activation of glial cells were identified, indicating the development of neurodegenerative processes. The resulting changes may be the morphological basis for cognitive impairment and emotional disorders in chronic stress.

The results of the study expand our understanding of the pathogenesis of stress-induced hippocampal lesions and can be used in the development of preventive and therapeutic approaches.

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