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RESEARCH ARTICLE

Assessment of Neurospecific Metabolites State Under Experimental Immobilization Stress

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Abstract: The leading pathogenetic mechanisms of stress development are associated with deterioration of human functional state, subsequent decrease in work performance, and disease development. The relevance of studying immobilization stress and using the ELI-Neuro-Test is driven by the need to understand the mechanisms of organism adaptation to extreme exposures and to diagnose early pathological changes. The most promising markers for identifying changes associated with chronic immobilization stress are antibodies to NF-200 and antibodies to the voltage-gated calcium channel (V-GCC). These assessment criteria will be more informative when included in a multifactorial diagnostic panel.

Key words: Immobilization stress, ELI-Neuro-Test, adaptation of the organism, antibodies, neuron-specific metabolites.

INTRODUCTION

The problem of the health status of modern humans has become particularly relevant due to the progressive spread of chronic stress in practically healthy individuals, resulting from the expansion of professional activity spheres, increased pace of life, lack of physical activity, environmental pollution, abuse of medications, tobacco, alcohol, etc. Prolonged and intense stressors of various natures lead to changes in many physiological processes; all systems of the human body respond to stress, including the nervous, immune, endocrine, cardiovascular, reproductive, and others (1,2,3). Under conditions of constant exposure to various stressors, adaptive mechanisms are constantly in a state of tension, which sooner or later leads to their exhaustion, and consequently, to the manifestation of the reverse side of the stress phenomenon – distress, during which adaptive reserves are depleted (Selye H., 1979). Thus, under modern conditions, stress transforms from an adaptive phenomenon into a link in the pathogenesis of various diseases, accompanied, in particular, by dysfunction of the nervous and immune systems as a single integrative block of regulatory mechanisms of the stress reaction (4,5,6,7).

Immobilization stress induces changes characteristic of civilization diseases: activation of the sympatho-adrenal system, increased corticosteroid levels, metabolic disorders, and the development of insulin resistance (9).

The leading pathogenetic mechanisms of stress development are associated with deterioration of human functional state, subsequent decrease in work performance, and disease development. It has been established that the development of PS (presumably "stress syndrome") is associated with increased production of central

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(adrenocorticotropin) and peripheral (cortisol) stress hormones. This is accompanied by impaired cerebral blood flow, preceded by endothelial dysfunction, decreased secretion of vasodilators involved in the activation of glutamatergic and serotonergic interneurons. The mechanism is associated with impaired neurovascular coupling, leading to disruption of adequate regulation of brain microcirculation under conditions of neuronal activity (8).

The relevance of studying immobilization stress and using the ELI-Neuro-Test is driven by the need to understand the mechanisms of organism adaptation to extreme exposures and to diagnose early pathological changes.

Purpose of the research

The aim of the study was ROC analysis of the diagnostic significance of neuron-specific metabolites by determining the concentration of IgG class autoantibodies interacting with central nervous system neuron antigens during acute and chronic immobilization stress.

METHODS

The study used 120 white outbred male rats with an initial weight of 200-220 grams. The animals were kept in the vivarium of the Tashkent Medical Academy at room temperature with a 12-hour light/dark cycle, free access to water and food, on a standard diet in accordance with laboratory animal housing standards.

The experimental animals were divided into three groups. The first group consisted of intact animals (n=40); the second group included animals with acute immobilization stress (n=40); the third group consisted of rats with a model of chronic immobilization stress (n=40).

To model acute emotional-immobilization stress in the experiment, animals were subcutaneously injected with adrenaline at a dose of 25 mcg/kg body weight according to the method of Tsygan V.I. et al. (2018). The model of chronic immobilization stress was reproduced by restraining the animal in a metabolic chamber for 3 hours daily over 30 days (Olesha A.Ya. et al., 2013).

To assess the state of the central and peripheral nervous system, standard test systems of the ELI-Neuro-Test group (Immunculus Research and Production Center, Moscow, Russia) were used by enzyme-linked immunosorbent assay (ELISA) on an ELISA analyzer (HUMAN, Germany) according to the manufacturer's instructions. Using standard ELI-Neuro-Test systems, the serum content of neurotropic IgG class antibodies directed against the following nerve tissue proteins was studied: neurofilament protein-200 (NF-200), glial fibrillary acidic protein (GFAP), S-100 protein, myelin basic protein (MBP), voltage-gated calcium channel (VGCC), glutamate receptors (Glu-R), dopamine receptors (DA-R), GABA receptors (GABA-R), serotonin receptors (Ser-R), cholinergic receptors (ACh-R), DNA, β2 glycoprotein (β2-GP).

RESULTS AND DISCUSSION

ROC analysis of the diagnostic significance of the studied autoantibodies for distinguishing the acute immobilization stress group from the control group reflects the relationship between sensitivity and specificity of the test at various threshold values, with the area under the curve (AUC) serving as an integral indicator of diagnostic marker effectiveness. The obtained results show that the highest discriminatory ability is exhibited by the indicator anti-GFAP (antibodies to the specific astrocyte protein) with AUC = 0.73, which corresponds to satisfactory model quality and indicates significant differences between animals with acute immobilization stress and intact animals. Slightly lower, but also acceptable, predictive value was noted for anti-MBP (antibodies to myelin basic protein) (AUC = 0.70). The indicator anti-nicotinic AChR demonstrated AUC = 0.67, and anti-NF-200 (antibodies to axon protein) --- AUC = 0.63, indicating weaker diagnostic informativeness for these markers.

Collectively, these data suggest that in acute stress, the most informative are immunological shifts associated with receptor and myelin components of the neurohumoral response, whereas markers of axonal damage possess lower selectivity in this context.

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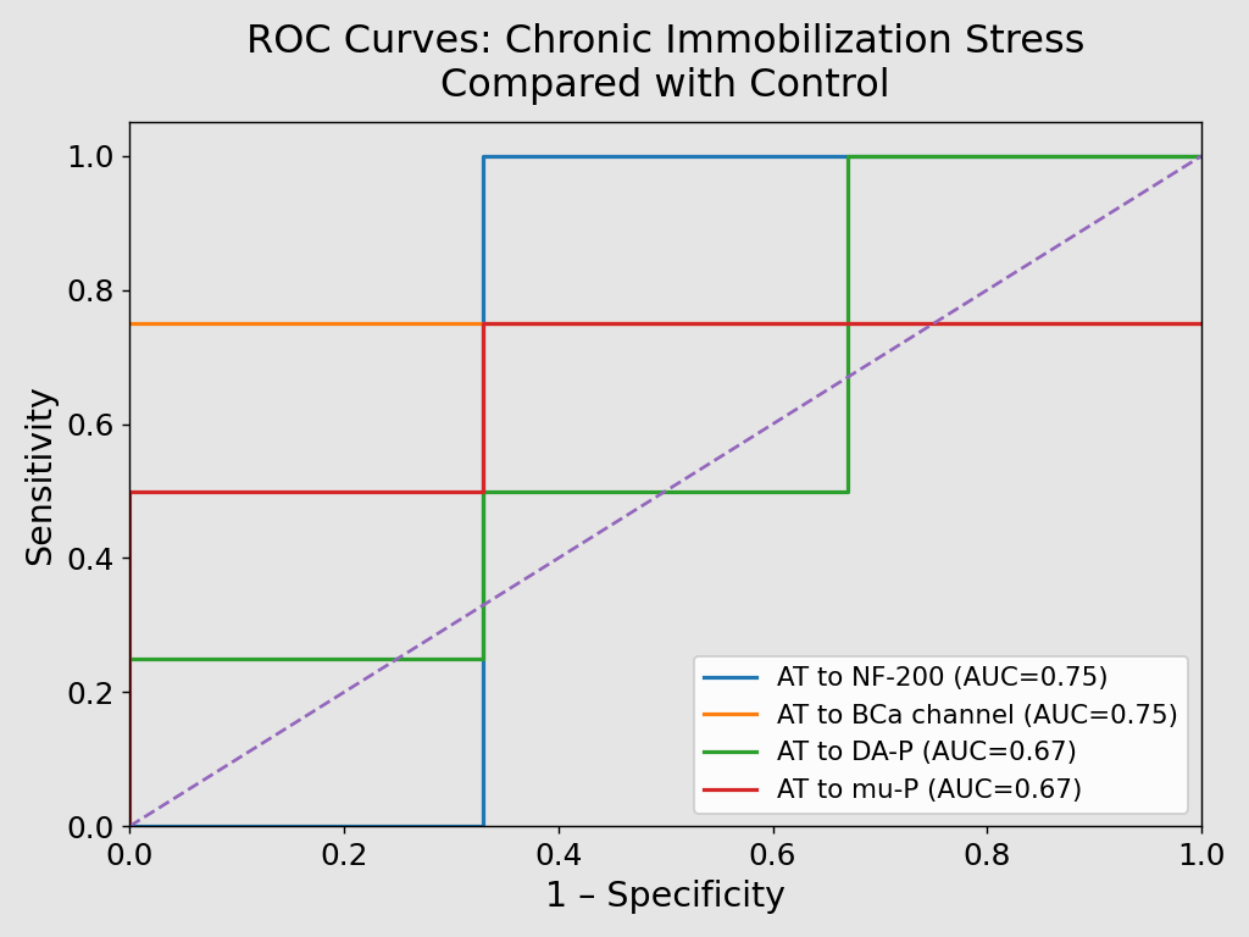
Figure 1 - ROC curves for diagnostic significance of autoantibodies in acute immobilization stress



ROC analysis of the diagnostic significance of the studied autoantibodies for distinguishing the chronic immobilization stress group from the control group established the highest diagnostic informativeness for anti-NF-200 and anti-VGCC, with area under the curve values of AUC = 0.75 for both. Such values correspond to statistically reliable diagnostic accuracy and indicate a comparatively better ability of these indicators to distinguish animals with chronic immobilization stress from values of intact animals.

At the same time, anti-GFAP was characterized by lower area under the curve values --- AUC = 0.67 in both cases. This indicates moderate diagnostic value of this marker and lower effectiveness of its use as an independent criterion for differentiating chronic stress exposure from physiological norm.

CONCLUSION

Thus, the most promising markers for identifying changes associated with chronic immobilization stress are antibodies to NF-200 and antibodies to the voltage-gated calcium channel (VGCC). These assessment criteria will be more informative when included in a multifactorial diagnostic panel.

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