THE FORMATION AND MAINTANANCE OF GASTRODUODENAL DYSRHYTHMIA ON THE BACKGROUND OF EXAGGERATED CELLULAR PROTEIC BIOSYNTHETIC ACTIVITY OF PARAVENTRICULAR, NORADRENERGIC, AND VAGAL CENTERS

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În prezentul studiu, citofotometria, citomorfometria şi metoda electrofiziologică au fost combinate pentru a examina starea funcţională a aparatului de sinteză proteică în celulele nervoase şi neurosecretorii centrilor reglatori în asociere cu activitatea mioelectrică în regiunile gastrice şi duodenale în caz de stresare acută şi cronică. Rezultatele obţinute au demonstrat că începutul perioadei de dezvoltare a stării de stres se caracterizează prin activizarea biosintezei în celulele neurosecretorii localizate în nucleul paraventricular al hipotalamusului. Această sporire a neurosecreţiei se asociază cu implicarea puţin mai tardivă a neuronilor din centrul noradrenergic trunchiular (*locus coeruleus*) în reacţia asupra stresării. Stresarea cronică duce la stabilirea activităţii biosintetice intensive în celulele nucleului dorsal al nervului vag şi în neuronii preganglionari din aria sacrală a măduvei spinării. Această distribuţie a activităţii centrilor de reglare neuronală condiţionează formarea şi stabilirea disritmiei motorice gastroduodenale. Activitatea exagerată a structurilor celulare hipotalamice şi noradrenergice poate asigura reducerea activităţii mioelectrice gastrice, dar cea a nucleului dorsal al nervului vag duce la stimularea activităţii mioelectrice duodenale.

Depression scores as a result of chronic psycho-emotional stress have a negative linear correlation with the electrogastrogram (EGG) resting frequencies. Anxiety scores have a positive linear correlation with the EGG area power ratio of the resting to stress responses. Cold or emotional stress affects gastric myoelectrical activity. Audio stimulation, with both music and noise, alters the rhythmicity and regularity of gastric slow waves [1]. During arithmetic task, the gastric power significantly increases [4]. Hyperactivity of gastric motility and the decrease in gastric mucosal blood flow play an important role in inducing gastric mucosal lesions under stress conditions. Regular gastric motility in antrum abolishes, for instance, after traumatic stress [2]. Obvious enhancement in gastric motility is induced in another stress model (the restraint plus water-immersion stress) [6]. Inflammation process developed as a result of stress could be associated with decreased colonic normal mixing motor patterns but increased propulsive motility including high amplitude propagated contractions. Stress-induced colonic motility is increased during diarrhoea associated with irritable bowel syndrome on the background of hyperresponsiveness to corticotrophin releasing factor (CRF) [5]. The role of CRF in gastrointestinal motility regulation represents a great importance. The brain CRF_1 receptors mediate the stimulation of colonic transit. CRF_2 receptors mediate the inhibitory actions of these peptides on gastric transit. Centrally administered CRF inhibits gastric emptying and contractility while simultaneously increasing colonic motility, transit and defecation, mimicking the gastrointestinal motor alterations observed in response to various stressors [3].

Thus, the aim of this study is to investigate myoelectrical gastroduodenal activity formed on the background of regulatory centers functional state under stress conditions.

This investigation was carried out by the utilization of cytophotometrical, cytomorphometrical, electrophysiological approaches in the rat. The restraint stress model was realized in wire mesh restrainers over 1-, 3-hour, 15-, and 30-day periods. Gallocyanin-chrome alum staining was applied for nucleic acids (NA) revealing. Nucleic acids optical density (D_{NA}) was measured cytophotometrically but NA quantity (Q_{NA}) was calculated for each cellular compartment in dependence on volume determined morphometrically. Electrogastrogram (EGG) was recorded by means of 12-channel electroencephalograph equipped by digital recorder "Spike" and special software for spectral EGG analysis. Electrophysiological investigation was realized at The Utrish Marine Biological Station (A.N. Severtsov Institute of Ecology and Evolution, Russia). Statistical analysis includes ANOVA test.

The obtained results of the morphometric and cytophotometric examines manifested that in the neurosecretory cells of the hypothalamic nuclei tested (paraventricular hypothalamic nucleus, PVHN, and supraoptic hypothalamic nucleus, SOHN) cytoplasmic RNA content is significantly enhanced (by 27.3%, $P<0.01$ and 19.6%,

P<0.05, respectively) at the 1-hour point after stress action beginning. The nuclear nucleic acid level in PVHN`s neurons is decreased by 21.5% (P<0.05). After 3-hr period of stressor action in the cytoplasm of neurosecretory cells in PVHN the nucleic acid quantity is decreased by 22.4% (P<0.05). The nucleic acid content remains increased by 17.5% (P<0.05) in the neuronal nucleolus on the background of nucleolus volume reduction. The cytoplasmic RNA content is restored up to baseline after 3 hr-period of stressor action in SOHN`s neurons.

The chronic action of restraint stressor (Fig.1) leads to significant changes of the protein synthetic activity and morphometric indices of hypothalamic neurosecretory cells. The cellular biosynthetic apparatus is attenuated after 15-day periodic stressor action. The cytoplasmic RNA level in PVHN`neurons is lower by 36.7% than baseline. The cytoplasm and nucleolus volumes are also reduced (by 18.3 and 16.3%, respectively). In the brain stem noradrenergic centre (locus coeruleus, LC) the neuronal biosynthetic apparatus activation is realized later than that in PVHN. Nevertheless, the protein biosynthesis is intensified after 1-hr stressor action in accordance with the nuclear nucleic acid level elevation (by 24.2%, P<0.05). After 3-hr stressor action the biosynthesis intensification is extended up to cytoplasm and is manifested by the cytoplasmic RNA level elevation (by 39.1%, P<0.01) and cytoplasm volume enhancement (by 23.3%, P<0.05). The chronic restraint stressor action (Fig.1) promotes the maintenance of enhanced protein biosynthetic activity in the noradrenergic neurons from LC. However, this intensified activity is manifested by the nucleic acid content increase in the neuronal nucleolus (by 25.1%). Finally, the nucleic acid quantity reduction is realized in the neuronal cytoplasm as a result of chronic stressor action (by 17.6%, P<0.05). In the case of chronic stressor action evident response of neurons from dorsal motor nucleus of vagus (DMNV) is revealed. In these neurons cytoplasmic RNA level is shifted (by 17.3%) after 15-day period of stressor action. Moreover, long-lasting preganglionic neuron biosynthetic

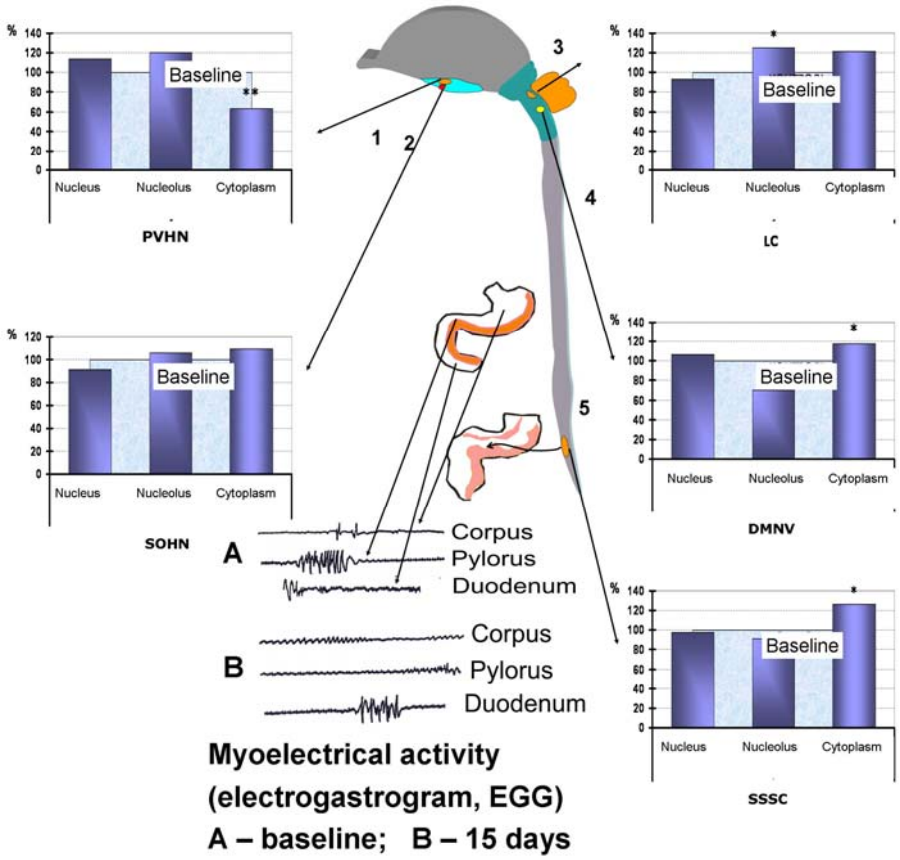

Fig.1. Biosynthetic activity in neuronal regulatory formations (nucleic acid content) and myoelecrical activity patterns after 15-day restraint stressor action (%).

1 – paraventricular hypothalamic nucleus (PVHN); 2 – supraoptic hypothalamic nucleus (SOHN); 3 – locus coeruleus (LC); 4 – dorsal motor nucleus of vagus (DMNV); 5 – sacral section of spinal cord (SSSC).

apparatus activation in the sacral section of spinal cord is also for interest. This activation is manifested by the earlier elevation of nucleic acid level in the neuronal nucleus and the later shifting in the cytoplasm (by 17.3%, $P<0.05$) after 30-day of chronic stressor action.

Recently, it was shown that the "wear and tear" resulting from chronic overactivity or underactivity of physiological stress response systems. Stressors which have been associated with such maladaptive consequences, both acute and chronic, are referred to pathological stressors [3]. The neurosecretory cellular elements of hypothalamic nuclei and noradrenergic neurons from LC shown to be included in the systems responded to different stressors. Therefore, evident morpho-functional modifications are manifested in these structural formations in association with stress-reaction development. Moreover, these modifications represent adequate criteria for estimation of stress restructurings dynamics. These restructurings in turn involve not only nervous and endocrine regulatory systems but also immune system. It is for interest that nucleic acid content changes dynamics evidenced by present study in subcellular compartments of PVHN and MDNV neurons close correlated ($r=0.659-0.757$, $P<0.05$). These findings confirm the close interaction between neuroendocrine and autonomic regulatory centers providing stress-reaction development. It is known, that in addition to sympathetic pathways activation the characteristic biphasic pattern of parasympathetic activity is forming during stress-reaction development. This biphasic pattern of parasympathetic activity consists of gastro-vagal inhibition and activation of the parasympathetic sacral efferent output [5].

In the present study phasic changes of gastro-duodenal myoelectrical activity are revealed on the background of enhanced biosynthetic activity in neurosecretory hypothalamic cells, and phasic activity in the noradrenergic centre, dorsal vagus nucleus and sacral spinal cord section. At the earlier stage of restraint stress-reaction development (1-3 minutes after stressor action beginning) the inhibition of EGG slow-wave activity is evidenced. This inhibition is manifested by the percentage reduction of the normal slow-wave activity (2.5-4 cpm, cycles per minute) presence in EGG recorded in stomach (up to 60% versus 73%, baseline, $P<0.05$). The spike activity predominance is evidenced in duodenal region after 1-hr stressor action (by 130% in comparison with baseline). This predominance is manifested by enhancement of oscillations amplitude and dominant frequency (5.3-7.4 versus 4.1-5.3 cpm baseline). After 5-hour stressor action myoelectrical activity dyscoordination is exaggerated in stomach sections, on the one hand, and in duodenal region, on the other hand. Following EGG recordings revealed that the myoelectrical activity dyscoordination between duodenal and pylorus regions is elevating during restraint stress development (after 15-day and 30-day stressor action). The dominant frequency averages 3.15-4.36 cpm in the duodenum region, and 2.81-2.9 cpm in the pylorus. This myoelectrical dysrhythmia suggests possible duodeno-gastric reflux development.

Therefore, acute restraint stressor action leads to biosynthetic apparatus activation in paraventricular neurosecretory cells, and neurons of noradrenergic brain stem centre on the background of myoelectrical gastric activity inhibition. Chronic stressor action result in cellular biosynthetic attenuation in paraventricular area and intensification in noradrenergic and vagus nuclei in association with profound myoelectrical dysrhythmia in gastroduodenal regions. Moreover, preganglionic sacral neurons are active over period of stressor chronic action.

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