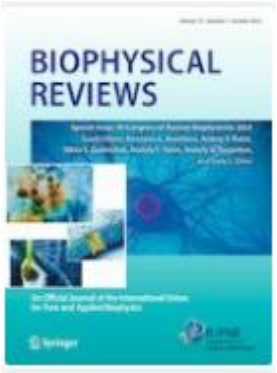

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Abstracts

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into the interior. In addition, dystrophin and the dystrophin associated glycoprotein complex play an important role in coordinating the work of various signaling systems, including ion channels that ensure the normal functioning of skeletal muscles, and the loss of these structures leads to dysregulation of ion homeostasis [1].

Currently, research is ongoing aimed at creating a gene therapy that can restore the normal expression of dystrophin. However, such approaches often face multiple technical problems, primarily due to the delivery of the vector, and can only be effective if therapy is started early, before the irreversible replacement of muscle tissue with non-functional connective tissue. In this regard, much attention is paid to the correction of the secondary effects of DMD, primarily the disruption of Ca2+ homeostasis associated with an increase in the amount of reactive oxygen species (ROS), chronic inflammation, a decrease in regenerative capacity, and fibrosis [1]. Mitochondria deserve special attention, providing muscle cells with energy in the form of ATP, which is necessary for normal contraction. During the development of DMD, these organelles demonstrate a significant decrease in the intensity of oxidative phosphorylation and hyperproduction of ROS, a decrease in the biogenesis of organelles and a violation of their dynamics [1]. In addition, a number of our works demonstrated that the mitochondria of skeletal muscles of dystrophin-deficient mdx mice are characterized by rearrangements in the systems of calcium and potassium transport [2, 3]. In particular, such changes are accompanied by a decrease in the efficiency of calcium uniport and sensitivity to the induction of the mitochondrial calcium-dependent pore (known as the MPT pore) [2], as well as inhibition of the transport of potassium ions and the content of this ion in the matrix of organelles [3]. We found that improving the ability of mitochondria to accumulate calcium ions in the matrix by using the non-immunosuppressive MPT pore inhibitor alisporivir leads to the normalization of mitochondrial function and ultrastructure, as well as a decrease in the intensity of destructive processes in skeletal muscles [4]. In addition, we have recently found that the activation of potassium ion transport in the skeletal muscle mitochondria of mdx mice using uridine, a precursor of the ATP-dependent potassium channel (mitoKATP) activator UDP, leads to a significant decrease in the level of fibrosis in skeletal muscles [3]. A more pronounced effect was shown for NS1619, an activator of the mitochondrial calcium-activated potassium channel (mitoBKCa), which improved the transport and level of potassium ions in the skeletal muscle mitochondria of mdx mice, which also contributed to a decrease in the intensity of oxidative stress and an increase in the calcium capacity of organelles, and was also accompanied by an improvement in the ultrastructure of organelles and mitigation of degenerative processes in the skeletal muscles of animals [5]. This report discusses the role of dysfunction of calcium and potassium ion transport systems in skeletal mitochondria in the development of Duchenne dystrophy, as well as the possibility of correcting this pathology by improving the function of these structures.

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References:

1. G. Angelini, G. Mura, G. Messina. Exp. Cell Res. 2022, 410, 112968.
2. M.V. Dubinin, E.Y. Talanov, K.S. Tenkov, et al. Biochim Biophys Acta Mol Basis Dis. 2020, 1866, 165674.
3. M.V. Dubinin, V.S. Starinets, N.V. Belosludtseva, et al. Int. J. Mol. Sci. 2022, 23, 10660.
4. M.V. Dubinin, V.S. Starinets, E.Y. Talanov, et al. Int. J. Mol. Sci. 2021, 22, 9780.
5. M.V. Dubinin, V.S. Starinets, N.V. Belosludtseva, et al. Pharmaceutics 2022, 14, 2336.

S9.724. The role of gravitational and muscular forces in the bone tissue remodeling

Baltina T.V.[1]*, Sachenkov O.A.[1]
[1] *Kazan Federal University;*
* tvbaltina@gmail.com

It is believed that the main regulators of mechanical bone transduction are exogenous gravitational forces and endogenous muscle forces. It's known, that changes in bone tissue are distinctive aspect of prolonged immobilization after injuries. In this case it is assumed that neuromuscular apparatus disorder leads to changes in the mechanical properties of muscle tissue and then to changes in the mechanical properties of bone tissue. But still, there is no convincing evidence of the muscle leading role in the regulation of bone tissue metabolism.

The H.M. Frost's mechanostat theory postulates a linear relationship between load and bone strength. According to the mechanostat theory local elastic deformation control bones adaptation processes. The origin of the local elastic deformation can be gravity or muscle strength. In case of gravity load some clarification should be mentioned. Gravity influence can be divided by mass and reactive loading. Reactive loading appears by foot support and can disappear in case of physical activity decrease. Meanwhile, mass loading can disappear only in case of weightlessness [1]. Then, H. M. Frost clarified the interrelation of the mechanostat system elements by including the influence of the nervous system, muscle contractions and mechanical loading (e.g. physical activity or foot support). Additionally, non-mechanical agents which affect modeling and remodeling were divided by systemic and local. So, the crucial question is what factor influences greater on activating mechanotransduction process? The answer can significantly improve the quality of clinical treatments. In this case, the physical medicine treatment can be designed for bone tissue restoration.

Bone loss is a common accompanying disease in clinical practice. E.g., patients with Duchenne muscular dystrophy or cerebral palsy suffer with bone mass loss and an increased risk of fractures [2,3]. In addition, significant bone loss occurs in patients with spinal cord injury [4,5]. Non-use of the hind limbs because of injury, immobilization (e.g. bed rest) or space flight lead to significant loss of bone and muscle tissue [6,7].

Bone loss appears in hind limb unloading models [8], additionally macromechanical and structural changes appears [9]. Studies of microgravity, unloading or non-usage (e.g. muscle tenotomy, denervation) models allows us to better understand the bone remodeling mechanism And leads to a new assumption - that biomechanical evolution can influence the remodeling process. Due to the modern data, it can be assumed that the signaling pathways responsible for influencing the morphology and function of muscles and bones are joint and consistent [10].

However, most gravity-related activities also require muscular effort (e.g. running, jumping). Opposite, some activities stimulate the skeleton almost exclusively due to muscle load (e.g. lifting weights, swimming), so it is important to evaluate the nature of the load. Determining the main stimulus for an adaptive response at the macroscopic level (muscle forces or gravitational loads) carries the potential for developing physical exercises and treatment methods aimed at more effective bone mass increase, as well as optimizing existing rehabilitation and prevention programs for osteoporosis.

The research is focused on systematization widespread experimental models, measured parameters and received correlation between external physical influence, its nature and bone tissue remodeling.

Reference

1 Frost H. M. A 2003 Update of Bone Physiology and Wolff's Law for Clinicians. Angle Orthod. 2004. Vol.74. P.3–15.

2 Tsaknakis K., Jäckle K., Lüders K.A., Lorenz H.M., Braunschweig L., Hell A.K. Reduced bone mineral density in adolescents with Duchenne Muscular Dystrophy (DMD) and scoliosis. Osteoporos Int. 2022. Vol.33. P.2011-2018.
3 Won J.H., Jung S.H. Bone Mineral Density in Adults with Cerebral Palsy. Front Neurol. 2021. Vol.12:733322. doi: 10.3389/fneur.2021.733322.
4 Coupaud S., McLean A.N., Purcell M., Fraser M.H., Allan D.B. Decreases in bone mineral density at cortical and trabecular sites in the tibia and femur during the first year of spinal cord injury. Bone. 2015. Vol.74. P.69-75.
5 Antoniou G., Benetos I.S., Vlamis J., Pneumaticos S.G. Bone Mineral Density Post a Spinal Cord Injury: A Review of the Current Literature Guidelines. Cureus. 2022. Vol.14:e23434. doi: 10.7759/cureus.23434.
6 Stavnichuk M., Mikolajewicz N., Corlett T., Morris M., Komarova S.V. A systematic review and meta-analysis of bone loss in space travelers. NPJ Microgravity. 2020. Vol.6:13. doi: 10.1038/s41526-020-0103-2.
7 Yang H., Xu X., Bullock W., Main R.P. Adaptive changes in micromechanical environments of cancellous and cortical bone in response to in vivo loading and disuse. J Biomech. 2019. Vol. 89. P. 85-94.
8 Baltina T.V. Ahmetov N.F., Sachenkov O.A., Fedyanin A.O., Lavrov I.A. The Influence of Hindlimb Unloading on Bone and Muscle Tissues in Rat Model. BioNanoSci. 2017. Vol. 7. P. 67-69.
9 Gerasimov O.V, Kharin N.V, Fedyanin A.O, Bolshakov P. V., Baltin M.E., Statsenko E.O., Fadeev F.O., Islamov R.R., Baltina T.V., Sachenkov O.A. Bone Stress-Strain State Evaluation Using CT Based FEM. Frontiers in Mechanical Engineering. 2021. Vol.7: 688474. doi: 10.3389/fmech.2021.688474.
10 Avin K.G., Bloomfield S.A., Gross T.S., Warden SJ. Biomechanical aspects of the muscle-bone interaction. Curr Osteoporos Rep. 2015. Vol.13. P. 1-8.

S9.725. The role of heat shock 70kda protein A1 in bipolar affective disorder

Seregin A.A.[1]*, Krotenko N.M.[2], Dmitrieva E.M.[1], Smirnova L.P.[1]
[1]*Tomsk National Research Medical Center of the Russian Academy of Sciences Mental Health Research Institute;*
[2]*Siberian State Medical University , SSMU;*
* apocalips1991@mail.ru

Today, studies related to the search for proteins specific to depression, bipolar disorder (BD) and other mental disorders are gaining popularity all over the world. The search for such proteins reflecting characteristic changes in the pathogenesis of these diseases is promising. (English J. et al., 2010; Lakhan S., 2006; Domenici E., 2010). The review of the literature shows that the works existing at this stage using proteomic analysis are mainly represented by works on schizophrenia; there are a few works done with depression and bipolar disorder, but mostly on posthumous material. As a result of a previous comparative mass spectrometric study of blood serum proteins in patients with depression and bipolar disorder, as well as in healthy donors, proteins were identified: heat shock protein 1A (Heat Shock 70kDa Protein1A), (HSPA1A) - 70.052, and alpha-actin -2 (Actin, aortic smooth muscle) (ACTA2), – 42.009 Da. In the present work, a comparative study of the amount of these proteins in the blood serum of patients with depression and bipolar disorder, presumably involved in the pathogenesis of these disorders, was carried out.

A clinical and biological examination of the blood serum of 74 people was carried out. The study groups were formed from 30 patients with recurrent depressive disorder (F33), and 28 patients with bipolar disorder (F31). Diagnostic assessment and clinical verification of the diagnosis in patients were carried out by doctors of the clinic of the Mental Health Research Institute in accordance with ICD-10. The mean age of the patients was 40.33±14.1 years. Blood was taken from all examined in the morning on an empty stomach before the start of therapy. As a control group, 14 mentally and somatically healthy individuals were examined, comparable in sex and age, with the examined patients (mean age 32.6±2.2 years).

To determine the amount of the studied proteins, commercial kits for enzyme-linked immunosorbent assay were used according to the manufacturer's protocol. The content of heat shock protein 1A was determined using the SEB081Hu Enzyme-linked Immunosorbent Assay Kit For Heat Shock 70kDa Protein1A(HSPA1A) from Homo sapiens (Human) (Cloud-Clone Corp., USA), and the amount of alpha-actin-2 was determined using Human α-Smooth Muscle Actin (α-SMA) ELISA Kit from Homo sapiens (Human) (Cloud-Clone Corp., USA). The statistical significance of differences between groups was determined using the nonparametric Kruskal-Wallis test and the Mann-Whitney U-test.

As a result of statistically significant differences in the content of ACTA2 between patients with bipolar disorder (164.85[151.05;187.95] ng/ml), depression (166.875[146.535;194.775]ng/ml) and healthy individuals (165.75[160.425; 178.575]ng/mL) is off-white, pairwise comparisons also showed no difference. However, significant differences between the studied groups were found in the content of heat shock 70kDa protein1A (HSPA1A). Pairwise comparison revealed that these differences arise due to an increase in the level of this protein in patients with bipolar disorder (0.8356 [0.5948; 1.098] ng / ml), in comparison with healthy individuals (0.6135 [0.5123; 0. 7722]ng/ml, Mann-Whitney U Test $p = 0.016$). The HSPA1A protein belongs to a family of highly conserved heat shock proteins expressed or induced in response to various stressors. They are involved in the synthesis and transport of proteins, and when exposed to stress factors, they prevent misfolding and aggregation of proteins (Benarroch 2011). It is known that these proteins are involved in the embryonic development of the central nervous system, and also participate in neuroprotection preventing the death of neurons (Reed-Herbert et al. 2006). According to literature sources, immune disorders were found in bipolar disorder during acute episodes of mania or depression (Barbosa et al., 2014; Brietzke et al., 2009; Cunha et al., 2008; Ortiz-Dominguez et al. 2007 Tsai et al. 2012). Also in the study by K. Becking et al. was found to overexpress HSPA1A in monocytes of patients with bipolar disorder during a depressive episode (Becking K, et all, 2015). In addition, based on the data of the model of protein-protein interactions common for HSPA1A and brain beams (A.M. Humyra et all, 2022), it is highly likely that HSPA1A is involved in the pathogenesis of BD. However, there are works on the association of the HSPA1A protein with paranoid schizophrenia, which may indicate common pathogenetic processes in these diseases, and this issue requires further study. Thus, the HSPA1A protein may be directly involved in the pathogenesis of BD and be proposed as an additional paraclinical criterion for BD in the further study of its role in this pathology.

S9.726. The role of miRNA in the mechanisms of CNS plasticity and the possibility of using it for the protection of cognitive impairment

Grinkevich L.N.[1]*
[1]*Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg, Russia;*
* larisa_gr_spb@mail.ru

The main challenges in studying the molecular basis of long-term memory formation are associated with the multitude of signaling systems, the integration of which is necessary for successful learning, and the variety of regulatory processes that interact at the genome level. The latter include the regulation of gene expression through DNA-binding transcription factors, as well as epigenetic modifications that