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THE ROLE OF ADIPOSE TISSUE CELL ELEMENTS CONTAINED IN STROMAL VASCULAR FRACTION IN THE REGULATION OF THE NITROXIDERGIC SYSTEM

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Introduction. Endothelial dysfunction is a key factor in the development of many vascular diseases, including those associated with hypoxia and metabolic disorders such as type 2 diabetes mellitus (T2DM). It manifests as a decrease in nitric oxide (NO) bioavailability, a potent vasodilator, and the accumulation of factors promoting vasoconstriction. This leads to microcirculation disorders, vascular wall inflammation, atherosclerosis, and thrombosis. Perivascular adipose tissue (PVAT) plays a special role in regulating these processes by releasing adipokines, cytokines, and other bioactive molecules. In T2DM, endothelial dysfunction is exacerbated by oxidative stress, iNOS hyperactivation, and eNOS activity reduction. This underscores the relevance of studying adipose tissue cellular elements' role in nitroxidergic system regulation under hypoxia, along with exploring pharmacological modulation options. The stromal vascular fraction (SVF), derived from adipose tissue and containing these cellular elements such as mesenchymal stem cells, endothelial cells, pericytes, and macrophages, represents a promising therapeutic tool. By leveraging the regulatory functions of these elements, SVF can enhance NO bioavailability, reduce oxidative stress, and improve endothelial function in hypoxic and diabetic conditions, thereby increasing the effectiveness of regenerative therapies.

The aim of this work was to evaluate the role of adipose tissue elements in regulating nitroxidergic system parameters under hypoxia conditions.

Materials and methods. The study was conducted during 2023–2024 at the

Department of Pharmacology and Medical Formulation with Course of Normal Physiology, Zaporizhzhia State Medical and Pharmaceutical University, providing access to necessary equipment and qualified specialists.

The study involved 30 adult white male Wistar rats weighing 190 ± 15 g that underwent modeling of T2DM. Animals were divided into two groups: the main group of 15 rats with induced T2DM and the control group of 15 intact rats. Inclusion criteria were adult males without contraindications to experimentation and voluntary assignment. Rats with complications in the early modeling period, severe comorbidities, or behavioral abnormalities were excluded. The methodological framework included a comprehensive approach to assessing modulation effectiveness. Theoretical analysis involved reviewing scientific literature on nitroxidergic system regulation in hypoxia, forming the basis for the experimental program. Experimental methods encompassed T2DM induction via high-fat diet and streptozotocin, isolation of arterial segments with or without PVAT, tensometry for measuring contraction amplitudes, and evaluation of contractile responses under hypoxia. Instrumental methods included tensometry for analyzing vascular activity and real-time PCR for NOS isoform expression assessment.

Quantitative and qualitative results were evaluated using validated tools: nitrotyrosine immunofluorescence for nitrosative stress assessment and qRT-PCR for eNOS/iNOS mRNA expression. Statistical processing used SPSS Statistics 25.0 and Microsoft Excel 2021, including mean calculations, significance testing via Student's t-test, and correlation analysis, with results deemed significant at $p<0.05$.

Results of the study demonstrated that the presence of PVAT significantly influences nitroxidergic system parameters under hypoxia, with advantages observed in modulated conditions across all metrics. Initially, both groups showed similar functional states: hypoxic vasoconstriction amplitude in PVAT+ vessels was 72.4% in phase 1 and 29.3% in phase 2, indicating balanced regulation. In the main group (T2DM), suppression was evident: amplitude dropped to 50.4% in phase 1 and 1.1% in phase 2 in PVAT+ vessels, and further to 6.8% in phase 1 and 60.2% in phase 2 in PVAT- vessels, highlighting dysfunction in T2DM without PVAT. A similar trend

was observed in nitrotyrosine levels: average nitrosative stress in the main group increased to 32.7 mU/iff/mm² in PVAT+ and 41.8 in PVAT-, while in the control group it remained at 12.9 mU/iff/mm². Such significant increase in nitrosative stress in the main group is explained by metabolic disruptions exacerbating oxidative processes and impairing NO balance, which can be mitigated by SVF application containing adipose-derived elements that promote anti-oxidative effects.

NOS isoform expression also demonstrated higher modulation potential in the presence of PVAT. On the initial stage, the average level of mRNA expression in both groups amounted to 1.0000 r.u. for eNOS and iNOS, which reflected baseline equilibrium disrupted by T2DM modeling. In the main group, eNOS dropped to 0.0217 and iNOS rose to 7.2560 in PVAT-, reflecting pronounced imbalance due to hypoxia. Post-modulation, indicators approached 0.7720 for eNOS and 3.2890 for iNOS, nearing normal functional levels. In the control group, values were 1.0750 for eNOS and 1.1800 for iNOS, with less pronounced shifts. Such results are associated with the regulatory roles of adipose tissue elements, which SVF harnesses to restore NOS balance through paracrine signaling and cellular interactions. Quality of regulation, evaluated via functional metrics, also significantly improved in the main group, underscoring SVF's potential to enhance these outcomes in therapeutic contexts.

Comparative analysis of results confirms that PVAT-dependent modulation ensures more effective regulation across key parameters. Differences between groups were notable in functional state (up to 26.7 times suppression in phase 2), nitrosative stress (9.3 mU/iff/mm²), and NOS expression (5-fold iNOS increase). Discussion of results emphasizes the importance of adipose tissue elements in hypoxia responses, where PVAT maintains NO-mediated vasodilation, and their absence exacerbates dysfunction in T2DM. Pharmacological agents further modulate these effects, but SVF, enriched with these elements, offers a cellular therapy approach by reducing oxidative stress, promoting angiogenesis, and restoring endothelial integrity, as evidenced in related studies on vascular diseases.

Conclusions. Based on the data obtained, it can be concluded that a

comprehensive approach to nitroxidergic system modulation in hypoxia is highly effective and yields better results compared to conditions without PVAT. The program incorporating pharmacological methods and emphasizing adipose tissue roles ensures faster restoration of vascular function, significant nitrosative stress reduction, NOS isoform balance enhancement, and improved regulatory metrics. Techniques like tensometry, immunofluorescence, histochemistry, qRT-PCR, and PVAT analysis accelerate NO regulation and contractility restoration, critical for preventing complications like oxidative imbalance or endothelial dysfunction. This understanding directly links to the effectiveness of SVF, which contains these adipose-derived cellular elements and can be utilized to therapeutically modulate the nitroxidergic system, improving outcomes in T2DM and hypoxia-related disorders through paracrine effects and reduced inflammation.

Developed recommendations include targeted use of pharmacological agents with PVAT considerations and exploration of SVF-based interventions for clinical optimization. These measures can be implemented to enhance modulation under hypoxia, contributing to physiological recovery and therapeutic advancements. Thus, the results confirm the necessity of focusing on adipose tissue elements as a key component for successful nitroxidergic regulation, with significant implications for SVF applications in regenerative medicine.