Phosphoproteome and Ubiquitylome Dynamics in the Heart Ventricle of Mice Treated with a Glucagon-like Peptide 1 Receptor Agonist (Liraglutide)

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Metabolic syndrome (MeS) intricately intertwines physiological risk factors, heightening susceptibility to cardiovascular disease (CVD). The Cardiovascular-kidney-metabolic (CKM) syndrome underscores connections among obesity, diabetes (T2DM), chronic kidney disease, and the cardiovascular system. Glucagon-like Peptide 1 Receptor agonists (GLP-1RAs) exhibit therapeutic promise, offering multifaceted benefits in metabolic and cardiovascular health, including enhanced insulin sensitivity, regulated body weight, and cardioprotection (increased glucose utilization, enhanced cardiac output, and reduced apoptosis). Our study aimed to uncover how Liraglutide, a GLP1-RA, affects phosphoproteomics and ubiquitinomics in cardiac ventricles. Using mass spectrometry-based proteomics, we analyzed phosphosites and ubiquitination sites after a 30-minute Liraglutide (0.3 mg/kg) treatment. In cardiac ventricles, we identified 4,919 phosphosites within 6,724 phosphopeptides from 1,385 proteins. Post-treatment, 375 phosphosites showed hyperphosphorylation, while 75 sites showed dephosphorylation/hypophosphorylation. Ubiquitin/SUMOylation analysis revealed 249 ubiquitinated peptides (217 Ub-sites) across 85 protein groups, with 22 sites up-regulated and 6 down-regulated post-treatment. Liraglutide\'s impact on cardiac phosphoproteomics suggests mechanisms related to cardioprotection, including enhanced glucose metabolism, improved calcium reuptake in the sarcoplasmic reticulum to prevent calcium overload and apoptosis, and optimized cardiac function through regulated PKA activation for efficient repolarization. It also promoted hyperphosphorylation of sarcomere and desmosome proteins, stabilizing cardiac muscle function. Notably, 5 significantly regulated proteins by Liraglutide, including SERCA2A involved in hypertrophy and heart failure, exhibited both phosphorylation and ubiquitination changes. These findings provide insights into Liraglutide\'s initial mechanisms via PTM regulations and how it influences key signaling pathways, aligning with clinical observations in treating type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD). This work was partially supported by the Sao Paulo Research Foundation (FAPESP, grant 2022/16606-4 to JTL)

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