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PhD Dissertation

Entitled

IMPACT OF PHYSICAL INACTIVITY ON GLUCOSE METABOLISM AND SKELETAL MUSCLE SECRETIONS IN HEALTHY TRAINED RATS AND POTENTIAL COUNTERACTING EFFECTS OF EXERCISE AND PROTOCATECHUIC ACID

by

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Abstract

Modern societies have significantly transformed people's lifestyles, leading to a substantial increase in physical inactivity, which concerns 23% of adults and 81% of adolescents worldwide. Physical inactivity is a major factor contributing to the emergence of chronic diseases, most prominently Type 2 Diabetes (T2D), which exhibits a high prevalence in many countries. T2D is characterized by elevated blood glucose levels due to cells' responsiveness to insulin. The shift towards inactivity likely occurred more rapidly than the genome's capacity to adapt, resulting in the metabolic dysfunctions underlying the development of T2D. Skeletal muscle is crucial in the onset of these metabolic dysfunctions, not solely because of its high metabolic activity but also owing to its endocrine function. The skeletal muscle can release a range of proteins to establish communication with peripheral organs to regulate metabolism. Nevertheless, the T2D underlying mechanisms encompassing the detrimental alterations in muscle secretions resulting from physical inactivity still require a comprehensive understanding. In addition to physical activity, phenolic compounds, particularly protocatechuic acid (PCA), have the ability to affect insulin sensitivity and glucose metabolism. The contribution of PCA to the regulation of glucose metabolism and its potential synergy with physical activity still require exploration.

This study seeks to examine the shifts in metabolic processes that transpire in the transition from an active lifestyle to a state of physical inactivity, to ascertain the contribution of muscle secretions to these alterations, and to assess whether aerobic activity and PCA can ameliorate the adverse consequences linked to inactivity, independently and in combination. A five-arm trial was conducted on 47 healthy male Wistar rats, trained for 4-weeks (T0-T4), then randomly divided into 5 groups: 8-weeks physical inactivity without PCA (AT4) or with PCA (AT4-PCA); physical activity (1 hour/day, 5 days/week at 25 m/min) for 4 more weeks without PCA (AT8) or with PCA (AT8-PCA); and vehicle control (VC). The study continued for 12-weeks, sacrificed 6 rats at T0 and T4, 4 per group at T8, and 3 per group at T12. Body weight, feed intake, intraperitoneal glucose tolerance test (IPGTT), glucose, serum lipid profile, liver enzymes, serum insulin, muscle secretions (interleukin-6 (IL-6), insulin-like growth factor-1 (IGF-1), fibroblast growth factor-21 (FGF-21), myostatin, and irisin), phosphofructokinase (PFK) and hexokinase (HK) activity, muscle glycogen, pyruvate, and expression of insulin signaling pathways, glucose transporter type-4 (GLUT-4), lipoprotein lipase (LPL), adipose triglyceride lipase (ATGL), and fatty acid transport protein-4 (FATP-4) were analyzed in muscle at T0, T4, T8, and T12. Additionally, for the in vitro experiment, C2C12 myotubes were cultured and received four treatments: control, PCA, insulin resistance (IR), and IR-PCA. Conditioned media from treated C2C12 myotubes was used to incubate HepG2 cells and 3T3-L1 adipocytes. Glucose uptake and protein expressions of signaling pathways were analyzed in all three cell lines.

Aerobic activity for 4-weeks improved glucose tolerance, lipid profile, liver enzymes, enhanced muscular HK activity, LPL and ATGL expression, myokines (IGF-1, IL-6, and FGF-21), insulin signaling pathways, and reduced myostatin in muscle, but a greater improvement was observed after 8 weeks of physical activity. In contrast, the beneficial effects of physical activity disappeared after only 4-weeks of inactivity (at T8 and T12), resulting in a reduction of IGF-1, IL-6, HK activity, LPL, and ATGL expression and increased pyruvate, glycogen, myostatin, and FGF-21 in muscle, which led to a negative alteration of the signaling pathway and glucose metabolism. Further, PCA treatment for 8-weeks mitigated the negative effects of inactivity by modulating insulin, myostatin, FGF-21, glucose tolerance, and GLUT-4 expression. Combining PCA dose with training (8-weeks) improved irisin level, IRS-1 expression, glycogen, and reduced PFK. The in vitro experiment highlighted the potential of PCA to regulate the crosstalk between muscle and other organs, ultimately regulating glucose metabolism. GLUT-4 expression was increased in the liver and adipose cells cultivated in the conditioned media obtained from PCA-treated C2C12 myotubes, enhancing glucose uptake in both cells.

In conclusion, reduced muscle contraction due to inactivity hindered skeletal muscle secretions, negatively influencing insulin signaling pathways and increasing the risk for T2D via a potential disruption of organs-crosstalk. PCA was highlighted as a potential counteracting agent against the metabolic alterations associated with inactivity. In addition to advocating for a phenolic-rich diet and regular engagement in aerobic physical activity, these findings can play a pivotal role in shaping novel therapeutic and preventive strategies for T2D.

Keywords: Physical activity, physical inactivity, glucose metabolism, insulin resistance, type 2 diabetes, muscle secretions.