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The Intricate Connections between Ketone Body Oxidation, Glycogen Stores, Glycolysis and Energy Metabolism in Cardiac Tissue

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Abstract

In the cardiac context, glucose and glycolysis play pivotal roles in supporting anaplerosis and potentially influencing the oxidation of d-β-hydroxybutyrate (βHB). The presence of glycogen, serving as a reservoir for glucose, could also contribute to anaplerosis. To delve into the intricate connections between glycogen content, βHB oxidation, glycolytic rates, and their consequential impact on energy dynamics, an isolated rat heart model was employed. Hearts with high glycogen (HG) and low glycogen (LG) levels were perfused with 11 mM [5-3H] glucose and/or 4 mM [14C] βHB to assess glycolysis and βHB oxidation, respectively. Subsequently, freeze-clamping was carried out for glycogen and metabolomic analyses. The ratio of free cytosolic [NAD+]/[NADH] and mitochondrial [Q+]/[QH_2] was estimated using the lactate dehydrogenase and succinate dehydrogenase reactions. 31P-nuclear magnetic resonance spectroscopy was utilized to measure phosphocreatine (PCr) and inorganic phosphate (Pi) concentrations. Notably, βHB oxidation rates in LG hearts were found to be half of those in HG hearts, exhibiting a direct correlation with glycogen content. Remarkably, βHB oxidation led to a reduction in glycolysis across all heart conditions. In glycogen-rich hearts perfused solely with βHB, glycogenolysis was twofold compared to hearts perfused with both βHB and glucose. This latter group demonstrated elevated levels of glycolytic intermediates, specifically fructose 1,6-bisphosphate and 3-phosphoglycerate, alongside a higher free cytosolic [NAD+]/[NADH] ratio. The influence of βHB oxidation was further evident through heightened levels of Krebs cycle intermediates, such as citrate, 2-oxoglutarate, and succinate. Additionally, the total NADP/H pool increased, mitochondrial [Q^+]/[QH_2] decreased, and the calculated free energy of ATP hydrolysis (ΔGATP) was elevated. Intriguingly, while βHB oxidation exerted an inhibitory effect on glycolysis, the reserves of glycolytic intermediates remained intact, and cytosolic free NAD sustained its oxidized state. Furthermore, βHB oxidation in isolation not only amplified Krebs cycle intermediates but also resulted in reduced mitochondrial Q levels and an enhanced ΔGATP. In summation, our findings underscore the facilitating role of glycogen in promoting cardiac βHB oxidation through anaplerosis.

Keywords: Cataplerotic • Anaplerotic supplementation • Intra-myocardial glycogen

Introduction

The heart, an incredible organ tirelessly pumping blood throughout our bodies, requires a constant and efficient supply of energy to fulfill its vital function. Energy production in the heart involves a complex interplay between various metabolic pathways, including ketone body oxidation, glycogen utilization, and glycolysis. Understanding the intricate relationships between these processes is essential for unraveling the mysteries of cardiac energy metabolism and potentially developing novel therapeutic strategies for heart-related conditions. Ketone bodies, namely acetoacetate, β-hydroxybutyrate, and acetone, serve as an alternative fuel source for the heart when glucose availability is limited. Produced primarily in the liver during periods of fasting or carbohydrate restriction, ketone bodies are transported to the heart where they are metabolized to generate ATP-the cellular energy currency. This ability of the heart to switch between glucose and ketone bodies for energy production is crucial for maintaining its functionality during various physiological states [1-3].

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Description

Glycogen: A rapid source of glucose

Glycogen, the stored form of glucose, acts as a rapid response mechanism to meet the heart's energy demands during periods of increased workload or stress. When energy requirements rise, glycogen is broken down into glucose through the process of glycogenolysis. This glucose can then be quickly channeled into glycolysis a series of enzymatic reactions that convert glucose into pyruvate, generating ATP in the process. Glycolysis is particularly important during short bursts of high-intensity activity when energy needs surpass the heart's ability to rely solely on oxidative metabolism [4].

Glycolysis: Balancing efficiency and speed

Glycolysis occupies a central role in cardiac energy metabolism by providing a rapid means of ATP generation. It not only acts as an emergency response pathway during times of heightened energy demand but also plays a vital role under normal physiological conditions. While glycolysis is less efficient in terms of ATP production compared to oxidative phosphorylation, its advantage lies in its speed. Under conditions of low oxygen availability, such as during ischemia or hypoxia, glycolysis becomes essential for maintaining cardiac function by preventing ATP depletion [5].

Interplay and regulation

The interdependence of ketone body oxidation, glycogen content, and glycolysis in the heart is tightly regulated to ensure optimal energy production and utilization. Hormones, such as insulin and glucagon, play a crucial role in modulating these pathways based on the body's energy status. Insulin promotes glycogen synthesis and inhibits glycogen breakdown, while also

encouraging glucose uptake and glycolysis. On the other hand, glucagon stimulates glycogen breakdown and promotes ketone body production, enabling the heart to adapt to changing energy demands.

Clinical implications and future directions

The intricate balance between ketone body oxidation, glycogen content, and glycolysis is of paramount importance for maintaining cardiac health. Dysregulation of these processes has been implicated in various cardiovascular diseases, including heart failure, ischemia-reperfusion injury, and diabetic cardiomyopathy.

Advancements in our understanding of these metabolic pathways have led to innovative therapeutic approaches. Targeting specific enzymes or signaling pathways within these pathways holds promise for improving cardiac function and preventing or treating heart-related disorders. Additionally, the potential benefits of dietary interventions, such as ketogenic diets, in modulating cardiac energy metabolism are being explored [6].

Conclusion

The heart's energy metabolism is a dynamic and highly regulated process that relies on the interplay of ketone body oxidation, glycogen content, glycolysis, and other pathways. This interdependence ensures the heart's ability to efficiently generate ATP under various physiological conditions, ultimately sustaining its essential pumping function. Further research in this field promises to uncover new insights into cardiac metabolism and may pave the way for innovative therapies to enhance cardiovascular health.

Acknowledgement

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Conflict of Interest

None.

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