AMPK Activation Beyond Metabolism: Exploring Metformin's Role in the Intrinsic Cardiac Nervous System (ICNS) and Arrhythmogenic Remodeling

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Abstract

Metformin is widely prescribed for the treatment of type 2 diabetes mellitus and is increasingly associated with reduced cardiovascular morbidity and improved electrophysiological stability. These pleiotropic effects are commonly attributed to activation of AMP-activated protein kinase (AMPK), a central regulator of cellular metabolism, inflammation, and mitochondrial homeostasis. While AMPK-mediated cardioprotective mechanisms have been extensively studied in cardiomyocytes and vascular tissues, the potential influence of metformin-driven AMPK signaling within the intrinsic cardiac nervous system (ICNS), which is a distributed network of cardiac ganglia that modulates autonomic tone, conduction, and rhythm, remains poorly understood.

This working paper proposes an integrative mechanistic framework that links metformin-induced AMPK activation to modulation of ICNS neuroinflammation and downstream arrhythmogenic remodeling. Emerging evidence indicates that inflammatory signaling within intrinsic cardiac ganglia can alter neuronal excitability, autonomic balance, and cardiac electrophysiology, thereby contributing to atrial and ventricular arrhythmias. We hypothesize that AMPK activation in ICNS-associated neurons and glia-like cells attenuates pro-inflammatory pathways, improves mitochondrial resilience and redox balance, and stabilizes neurocardiac control circuits, ultimately reducing susceptibility to arrhythmogenesis.

Drawing on interdisciplinary literature spanning cardiometabolic pharmacology, neuroinflammation, autonomic neuroscience, and cardiac electrophysiology, this manuscript synthesizes current evidence supporting an "AMPK–ICNS–arrhythmia axis." We further outline testable predictions and future experimental priorities, including single-cell and spatial transcriptomic profiling of cardiac ganglia, inflammation-sensitive imaging approaches, and integrative neurocardiac electrophysiological studies. By positioning the ICNS as a critical intermediary between metabolic signaling and rhythm regulation, this framework aims to expand the conceptual scope of metformin's therapeutic action and identify novel neurocardiac targets for arrhythmia prevention.

Keywords: Metformin; AMPK; Intrinsic Cardiac Nervous System; Neuroinflammation; Arrhythmia; Cardiac Remodeling