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Enhancing Fatty Acids Oxidation *via* L-Carnitine Attenuates Obesity-Related Atrial Fibrillation and Structural Remodeling by Activating AMPK Signaling and Alleviating Cardiac Lipotoxicity

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Abstract

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical setting. Its pathogenesis was associated with metabolic disorder, especially defective fatty acids oxidation (FAO). However, whether promoting FAO could prevent AF occurrence and development remains elusive. In this study, we established a mouse model of obesity-related AF through high-fat diet (HFD) feeding, and used l-carnitine (LCA, 150 mg/kg·BW/d), an endogenous cofactor of carnitine palmitoyl-transferase-1B (CPT1B; the rate-limiting enzyme of FAO) to investigate whether FAO promotion can attenuate the AF susceptibility in obesity. All mice underwent electrophysiological assessment for atrial vulnerability, and echocardiography, histology and molecular evaluation for AF substrates and underlying mechanisms, which were further validated by pharmacological experiments *in vitro*. HFD-induced obese mice increased AF vulnerability and exhibited apparent atrial structural remodeling, including left atrial dilation, cardiomyocyte hypertrophy, connexin-43 remodeling and fibrosis. Pathologically, HFD apparently leads to defective cardiac FAO and subsequent lipotoxicity, thereby evoking a set of pathological reactions including oxidative stress, DNA damage, inflammation, and insulin resistance. Enhancing FAO *via* LCA attenuated lipotoxicity and lipotoxicity-induced pathological changes in the atria of obese mice, resulting in restored structural remodeling and ameliorated AF susceptibility.

Mechanistically, LCA activated AMPK/PGC1α signaling both *in vivo* and *in vitro*, and pharmacological inhibition of AMPK *via* Compound C attenuated LCA-induced cardio-protection in palmitate-treated primary atrial cardiomyocytes. Taken together, our results demonstrated that FAO promotion *via* LCA attenuated obesity-mediated AF and structural remodeling by activating AMPK signaling and alleviating atrial lipotoxicity. Thus, enhancing FAO may be a potential therapeutic target for AF.

Keywords: AMPK (5'-AMP activated kinase); atrial fibrillation; fatty acids oxidation; l-carnitine; lipotoxicity; obesity.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.